Synthesis of Cyclic α,β-Unsaturated Ketones *via* a Divergent Aldehyde Allylation and Ring-Closing Metathesis Method

by

Adam Kafal

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Department of Chemistry
University of Toronto

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Abstract

Montmorillonite-catalyzed allylation of aldehydes with potassium allyltrifluoroborate is a convenient method for the synthesis of homoallylic alcohols. This chemistry was applied to various unsaturated aldehydes, and the homoallylic alcohols produced were used as common intermediates for two separate but related synthetic routes to α,β-unsaturated ketones. In the first route, oxidation of the alcohol to the ketone was followed by base-catalyzed isomerization of the olefin to the α,β-unsaturated ketone. This was subjected to ring closing metathesis conditions to afford the cyclic enone of ring size *n*. In the other route, ring-closing metathesis was performed first, followed by oxidation of the alcohol and isomerization of the olefin to the cyclic enone of ring size *n+1*.

Acknowledgments

To the Batey lab:

To Prof. Rob Batey, for accepting me into his lab, maintaining a firm but calm demeanour in the face of my periodic spells of incompetence, and ultimately teaching me more about chemistry than anyone ever has. None of this work or what it represents would have been possible without him.

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And to that fortune cookie. Such optimism.

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List of Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
CM	cross-metathesis
Cy	cyclohexyl
dba	dibenzalacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
EI	electron impact
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
^{i}Pr	isopropyl
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital

Me	methyl
Mes	mesityl
MS	electron impact mass spectrometry
MVK	methyl vinyl ketone
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidine
NSAID	non-steroidal anti-inflammatory drug
Nu	nucleophile
OTf	trifluoromethanesulfonyl
p-BrBzO	*para*-bromobenzoyl
Ph	phenyl
PCC	pyridinium chlorochromate
RCM	ring-closing metathesis
R_f	retention factor
ROMP	ring-opening metathesis polymerization
salen	*N*,*N*'-ethylenebis(salicylimine)
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

Chapter 1
Introduction

1 Divergence in Organic Synthesis

It may be one of the more universal traits among organic chemists and our trade that we enjoy discussing the philosophy of our craft; thinking about how we think. After slightly archaic beginnings the field picked up momentum rather quickly in the 20th century and many a hobbyist-philosopher or otherwise scientist had his own ideas, inklings, and accidental moments of insight that hurried organic synthesis along in as many directions as there were chemists to take it there. Today, with the same free-spirited lust for probing the unknown, researchers are throwing themselves into their work with the hopes of discovering the next groundbreaking method or molecule. And though one would be remiss to suggest that we are necessarily being rather careless with our fast-paced modes of conduct, we can stand to be reminded of the provisos we are obliged to accept as responsible scientists. For example, an oft-touted notion of importance is the concept of atom economy.[1] A simple concept with far-reaching implications, this mode of evaluation aims to, in the simplest way possible, assign a quantifiable measure for any given chemical transformation in order to determine how efficient it is. Although it is seemingly common sense, this notion has become more and more formally respected, as is apparent from the modern chemical literature.[2]

A more recent and possibly controversial philosophy in the field has been *ideality of synthesis*: What score can we assign to this synthetic route? An in-depth manifesto of aiming for the ideal synthesis was recently published by Gaich and Baran.[3] Here, their formula is simple:

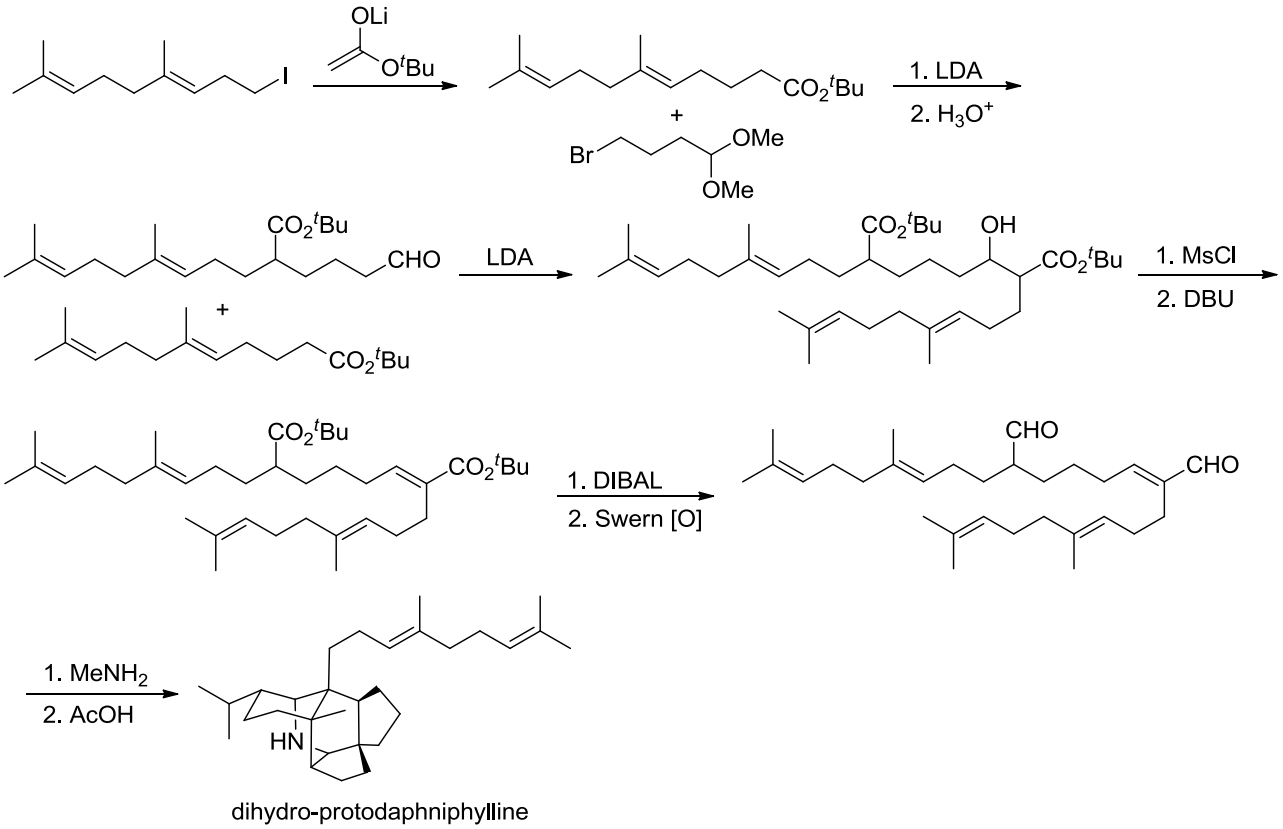
$$\%\ ideality = \frac{(\#\ construction\ rxns) + (\#\ strategic\ redox\ rxns)}{total\ \#\ steps} \times 100$$

Equation 1. Gaich and Baran's Ideality of Synthesis.

This is an interesting proposal, but a dangerous one. For example, Heathcock's famous 10-step synthesis of dihydro-protodaphniphylline (Scheme 1)[4] elicits a mere 50% ideality when evaluated with this method! If such groundbreaking elegance in synthesis is only half-perfect,

what besides nature itself could possibly ever come close to the 100% mark? Indeed, biosynthetic pathways themselves would also score low according to such parameters! Of course, these notions of atom economy and ideality of synthesis are not concrete rules, by any means. We are not limited by a simple formula when deciding how to conduct a synthesis. Nevertheless they retain a certain validity and the important lesson to take from these proposals — and moreover from the fact that scientists are even *making* these proposals so boldly — is that foresight, accountability, and overall efficiency are pillars of proper organic synthesis. One would be hard pressed to effectively debate the contrary.

Scheme 1. Heathcock's Total Synthesis of Dihydro-protodaphniphylline.



Rather than the departure from an established procedure, convention, or otherwise accepted directive, the designation *divergence in organic synthesis* can be applied to the utilization of some common intermediate as a branching point in the synthesis of two or more different yet

related molecules. A related concept is *convergence*, which is effectively the opposite process, creating a single product from two separate scaffolds. These are illustrated in Figure 1.

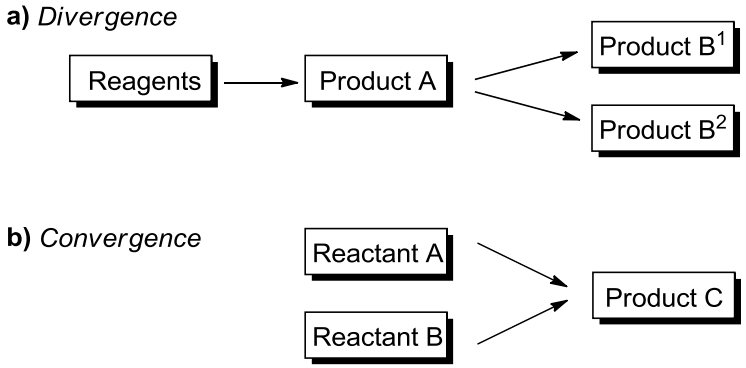


Figure 1. (a) Divergence from a Common Intermediate Leading to Two Distinct Products, and (b) Convergence from Two Distinct Species to One Product.

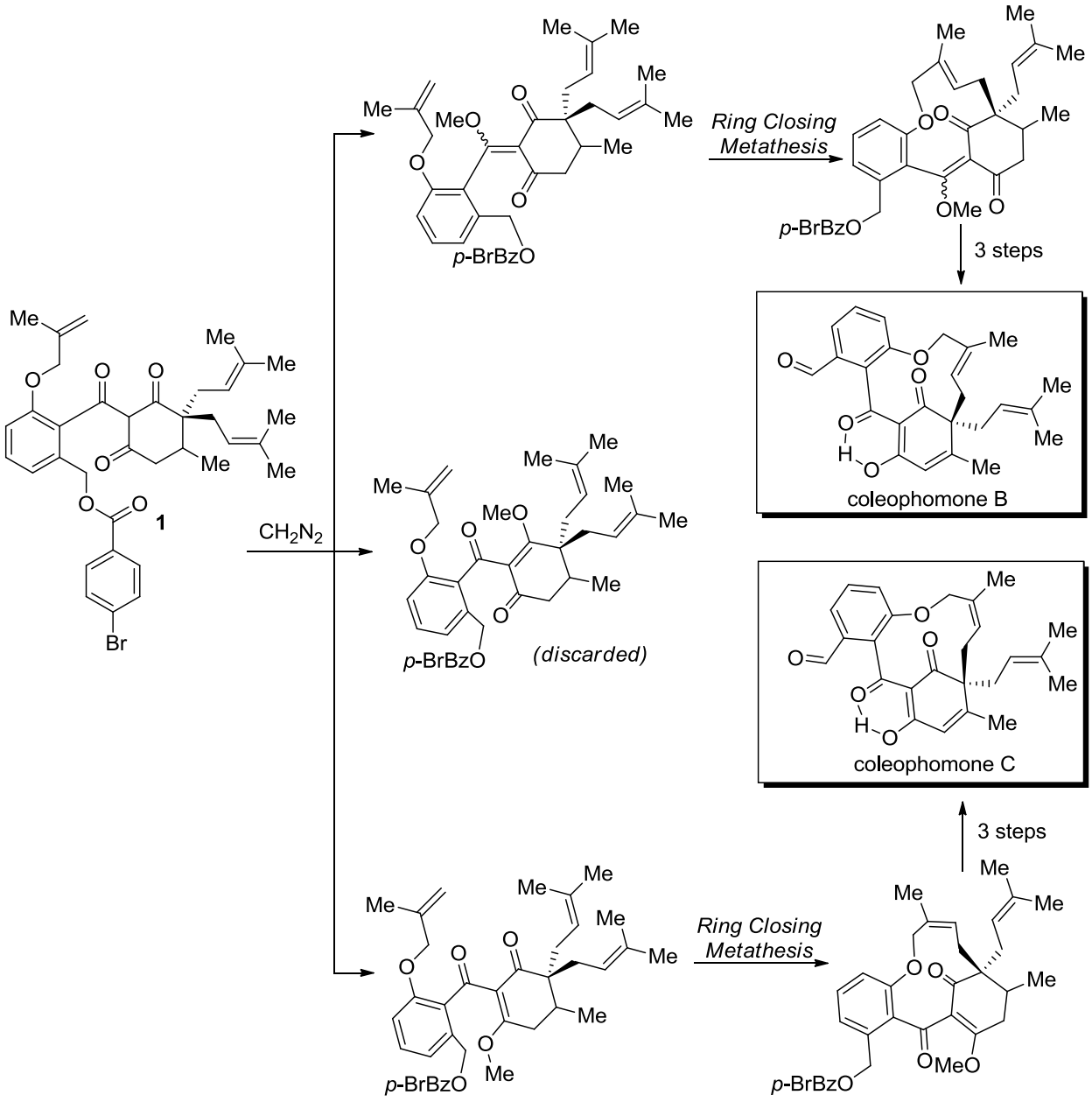
There has been a recent boom in target-oriented syntheses involving what has been dubbed *diversity-oriented synthesis* (DOS).[5] The strategy of DOS is to build as many different possible iterations of some carbon skeleton as easily and in as few steps as possible. This can be accomplished in several ways, including solid phase synthesis, and other traditional combinatorial methods.[5b] On the other hand, with *divergent* strategies, the focus is on smaller and more deliberate iterations of a common intermediate molecule, which is chosen specifically to furnish two or more targets relatively easily. And whereas DOS implies preparing many different molecules at the same time, a *divergent* scheme involves building a relatively large amount of *one* compound, splitting and then carrying this bulk material down several separate synthetic routes simultaneously with two different targets in mind. One is reminded of Yogi Berra's famous turn of phrase, "When you come to a fork in the road, take it!"[6]

Though not as quantitative as Equation 1, divergence is a methodological tool that we can use in efforts toward achieving the ideal synthesis, or at least toward approaching it. It is a simple concept, one that has been applied in numerous syntheses, but it has not been formally described as a stand-alone concept in any general sense (e.g., a review article). The following examples will aim to outline some of the successes of the tactic in organic synthesis.

In the total synthesis of coleophomones B and C, Nicolaou and co-workers were able to construct both targets from a single common precursor **1** (Scheme 2).[7] Following a diazomethane

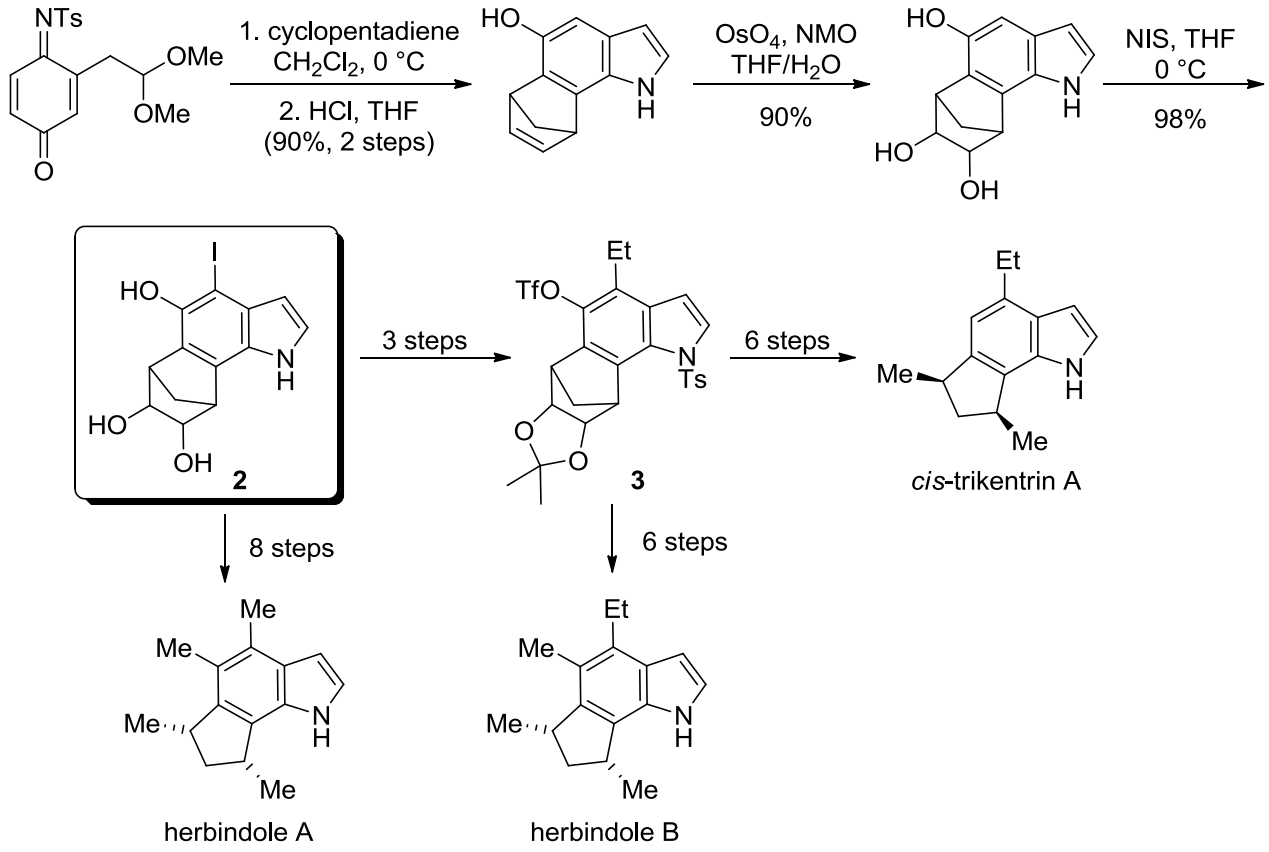
protection, this common precursor gave three products in a high overall yield (96%). Subjecting the two of these intermediates of interest to ring-closing metathesis (RCM) conditions with Grubbs' second-generation catalyst yielded two macrocycles in a remarkable regio- and stereospecific transformation. These two molecules were further elaborated to furnish the target molecules. Certainly with molecules of this size and complexity, embracing a divergent pathway was quite advantageous.

Scheme 2. Nicolaou's Divergent Approach to Coleophomones B and C.



In a divergent synthetic strategy towards quinine monoamine derivatives, Jackson and Kerr reported the total synthesis of (±)-herbindole A, (±)-herbindole B, and (±)-*cis*-trikentrin A.[8] The synthesis relied on a Diels-Alder reaction with quinoid imines to build the common iodoindole intermediate **2** (Scheme 3). This compound provided the molecular skeleton for all three targets, with herbindole A being furnished in fewest steps. In order to access the remaining two targets, they opted to employ yet another divergent step, building the common protected diol intermediate **3**. This was then elaborated *via* two separate pathways to herbindole B and *cis*-trikentrin A, requiring 6 steps each.

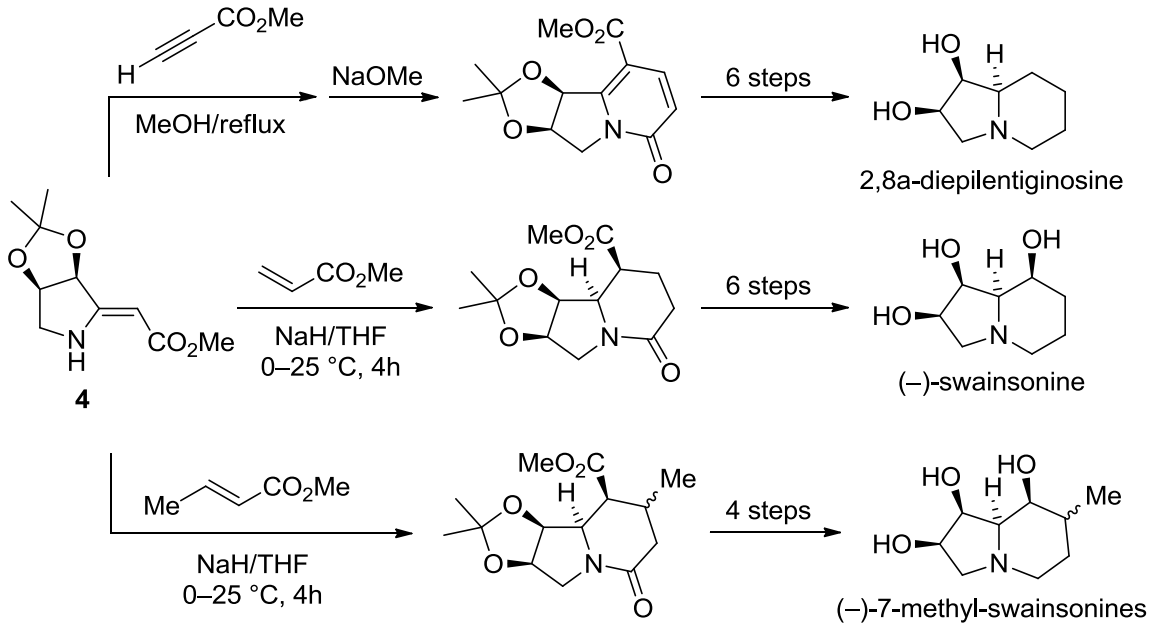
Scheme 3. Kerr's Divergent Approach to (±)-Herbindole A, (±)-Herbindole B, and (±)-*cis*-Trikentrin A.



A third example of divergence in total synthesis is one from Cheng and co-workers, who reported the concise synthesis of 2,8a-diepilentiginosine swainsonine, and 7-alkyl swainsonines *via* a chiral enaminoester intermediate (Scheme 4).[9] All three of these polyhydroxylated

indolizidine alkaloids were derived from isopropylidene-protected enaminoester **4**, which was prepared from D-erythronic acid γ-lactone. This work exemplifies beautifully the potential for simple, inexpensive starting materials to be used in simple divergent manipulations, rendering practical syntheses of numerous natural and unnatural products. This family of polyhydroxylated indolizidine alkaloids in particular has attracted a significant amount of attention owing to a broad spectrum of biological activities.[10] With such a potential for analogue studies, the divergent approach to this family of molecules opens numerous doors for biological studies.

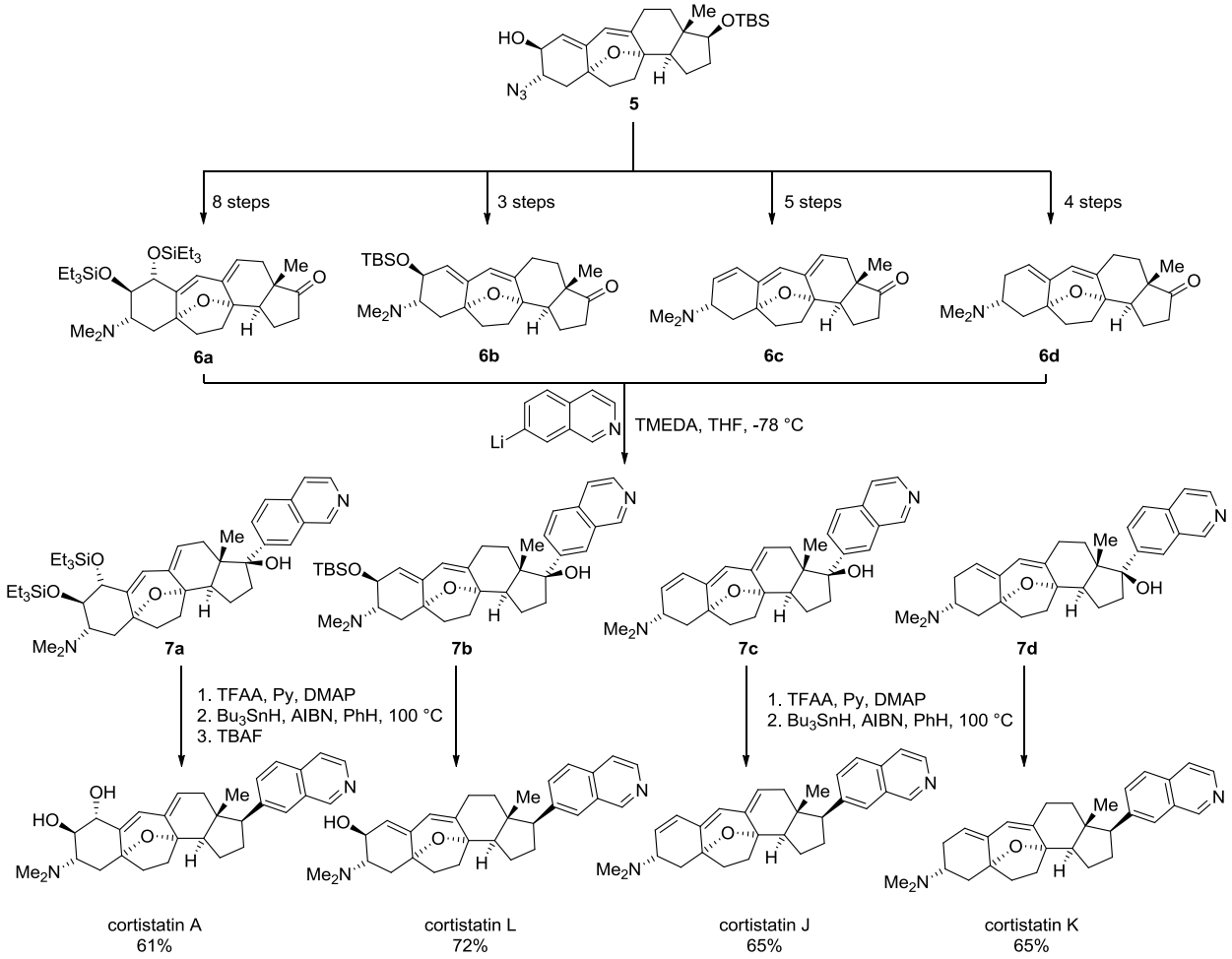
Scheme 4. Cheng's Divergent Approach to 2,8a-Diepilentiginosine, Swainsonine, and 7-Alkyl Swainsonines.



One of the most impressive examples of divergence is one from Myers and co-workers toward the synthesis of cortistatins A, J, K, and L. These modified-steroidal marine natural products have been the subject of synthetic and biological interest, and though cortistatins A and J had been synthesized previously,[11,12] the divergent approach employed by this group was the first to afford cortistatins K and L. Furthermore, all four compounds were accessed from a single common intermediate **5** (Scheme 5). This azido alcohol was elaborated *via* four separate paths of varying synthetic length in order to furnish cortistatin precursors **6**, at which point a parallel 17-keto addition of 7-lithioisoquinoline installed the isoquinoline moiety in each to yield compounds **7**. From here, identical reductive deoxygenations led to

cortistatins J and K directly from **7c** and **7d**, respectively, while a silyl deprotection was further required for access to cortistatins A and L, from **7a** and **7b** respectively.[13]

Scheme 5. Myers' Divergent Approach Toward Synthesis of Cortistatins A, J, K, and L.



Clearly, divergent synthetic strategies constitute a valuable approach in complex molecule synthesis and new methods that utilize divergent approaches will be valuable synthetic tools. While the method lacks the overall efficiency, and the raw analogue-producing power associated with related utilities such as DOS, the purposeful and calculated introduction of related functionalities in multiple directions from a single common intermediate remains a viable tool. It is appealing because it is simple, and powerful. Further, divergence has the capacity to be introduced into *any* appropriate synthetic plan, e.g., where biomedical / structure-activity relationship implications may be of interest.

2 α,β-Unsaturated Ketones

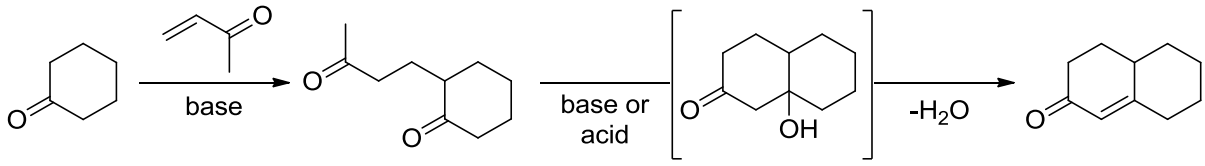
2.1 Modern Synthetic Methods Toward α,β-Unsaturated Ketones

The humble enone is a common motif, but it remains a notable and interesting one. Undoubtedly one of the most important functionalities in organic chemistry, each site of the requisite four atom sequence can, under appropriate conditions, function as a reactive centre. There was an especially rapid development of enone synthesis in the latter half of the 20th century, when intensive efforts arose toward the synthesis of various biologically active natural products. Many of these contain the enone functionality, while numerous others are accessed *via* an enone-containing intermediate.

2.1.1 Condensation

The first major route to enones, and still the most common, is through an aldol condensation. In 1935, Robinson discovered what is now known as the Robinson annulation, which involved the base-catalyzed Michael addition of an activated methylene group of cyclohexanone to methyl vinyl ketone (MVK), followed by base- or acid-catalyzed aldol condensation to give the enone (Scheme 6).[14] This named reaction now describes any such condensation reaction between a ketone (usually cyclic) and an α,β-unsaturated ketone to give a substituted cyclohexenone derivative.

Scheme 6. Classical Enone Synthesis: The Robinson Annulation.



The Robinson annulation suffers from a number of drawbacks, including low yields owing to polymerization of the Michael acceptor, as well as lack of regiocontrol in the case of unsymmetrical ketones. Today, a number of modifications to this classical reaction have been developed, including *in situ* generation of the Michael acceptor,[15] and asymmetric Michael addition.[16]

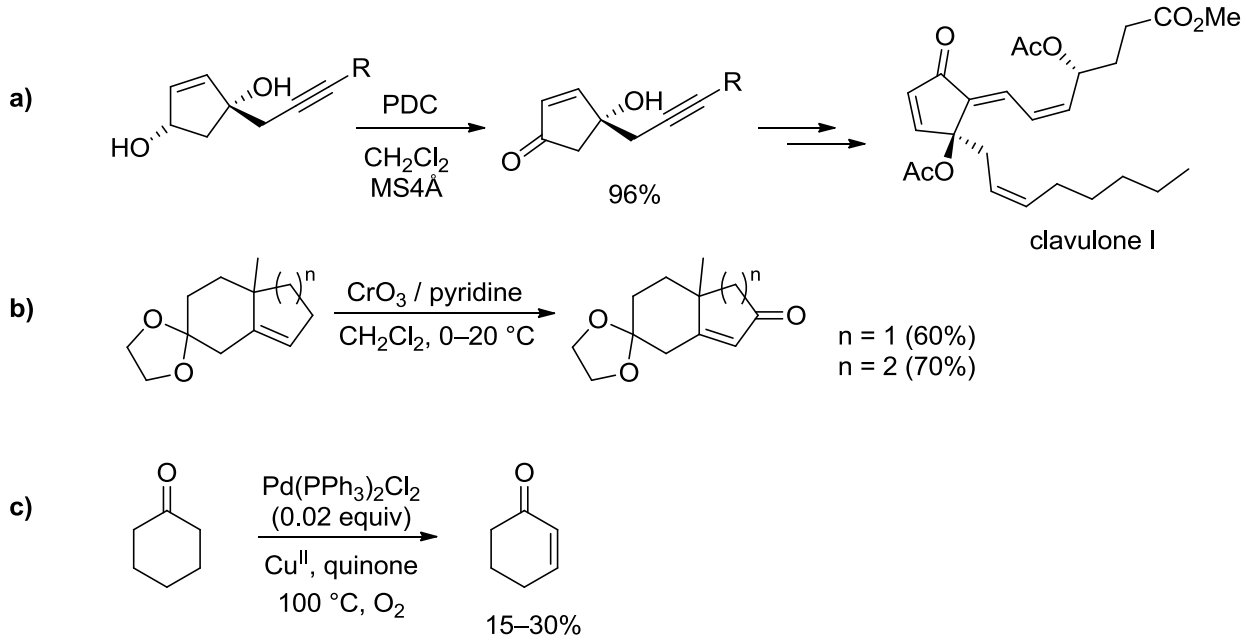
To complement the utilization of intramolecular annulations, as in the above case, there have been numerous investigations into intermolecular aldol condensations pertinent to enone generation. One example reported by Muzart uses a basic alumina catalyst to absorb the ketone starting materials where, after several days of reaction time on the alumina surface, the resulting enones are eluted.[17] Disadvantages of this intriguing method include low conversions, and slow reaction rates in the case of hindered ketones. In a slightly less radical, but still interesting example, lithium iodide has been found to promote the intermolecular aldol condensation between alkyl ketones and a number of enolizable and non-enolizable aldehydes. Using lithium iodide in ether, tetrahydrofuran, or benzene, α,β-unsaturated ketones can be obtained in 70−90% yields. It is notable that both the lithium and iodide ions are necessary; LiCl, LiBr, NaI, and KI are ineffective, and addition of crown ether also destroys this effect, ostensibly through complexation with the lithium cation.[18]

Other useful condensation routes to enones include Horner-Wadsworth-Emmons approaches,[19] using an α-silyl vinyl ketone Michael acceptor,[20] and proline-catalyzed Robinson annulations (commonly referred to as the Hajos−Parrish reaction).[21]

2.1.2 Oxidation

To furnish enones, oxidation reactions can be utilized in three general ways: (a) oxidation of allylic alcohols, (b) oxidation of allylic methylenes, and (c) oxidation of saturated ketones. Route (a) is most commonly used on account of its amenability to a variety of oxidizing agents, including pyridinium dichromate,[22] pyridinium chlorochromate,[23] and Dess-Martin periodinane.[24] Scheme 7a shows Corey's such use of PDC in his synthesis of clavulone I.[26a] Routes (b) and (c) are not utilized as frequently, often suffering from poor yields due to harsh reaction conditions and/or lack of regiospecificity, and for such reasons cannot be considered general.[25] Rare examples of route (b) include the allylic oxidation of cycloalkenes with Collins' reagent to yield the corresponding cycloalkenones (Scheme 7b).[26b] Route (c) is exemplified by Theissen's use of palladium (II) to dehydrogenate cyclic ketones of varying sizes (Scheme 7c).[26c]

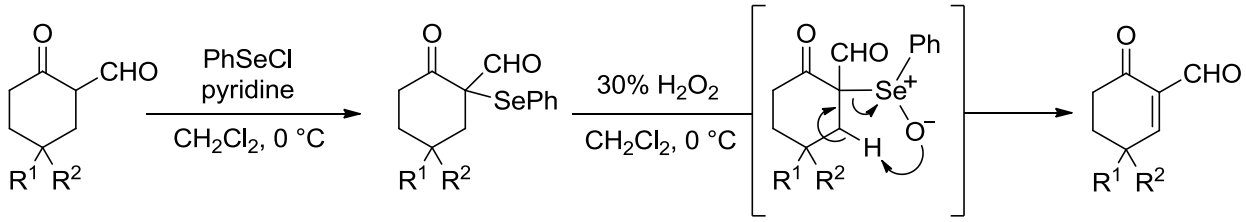
Scheme 7. Various Oxidative Routes toward Cyclic Enones.



2.1.3 Elimination

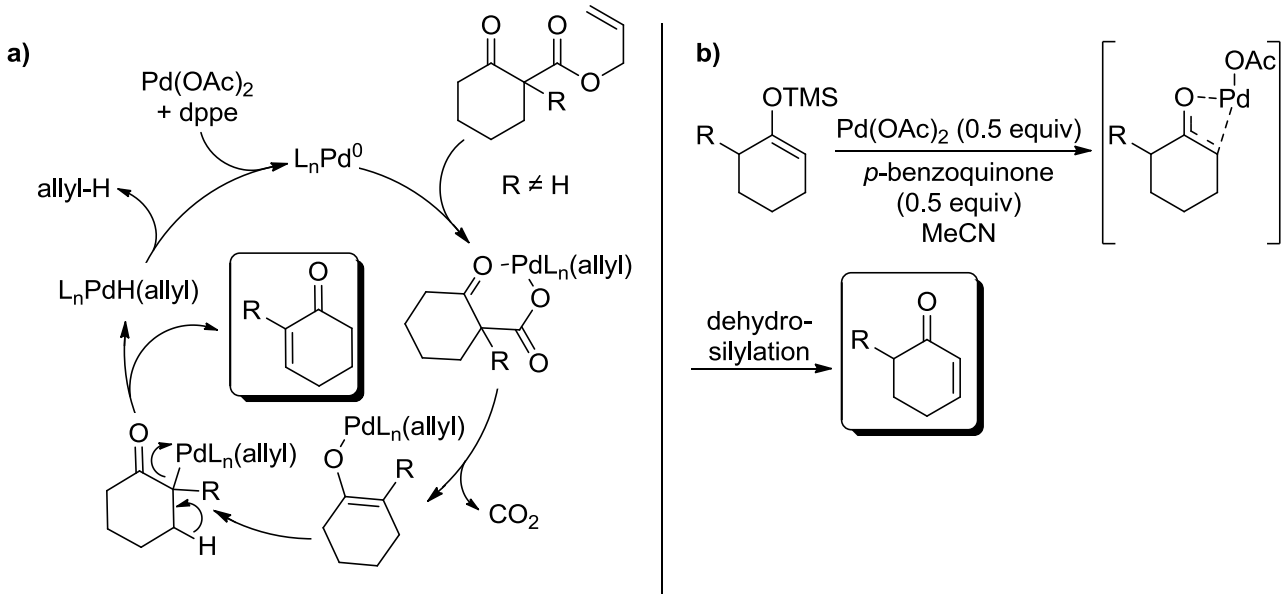
The use of elimination reactions in enone synthesis is very well established, among the most classical of which is an α-bromination/HBr elimination sequence.[27] More recent developments have improved this transformation, notably using selenium and sulfur compounds. Such modifications have allowed for milder reaction conditions with superior yields. An example of a useful application of this chemistry is shown in Scheme 8, where the target enones are generated in excellent yields (84–100%).[28]

Scheme 8. Selenium-Mediated Synthesis of Unsaturated β-Dicarbonyl Compounds.



There have been a number of palladium-catalyzed elimination reactions reported, beginning in 1983 with palladium acetate and 1,2-bis(diphenylphosphino)ethane as catalysts. The mechanism for this reaction is outlined in Scheme 9a.[29] In such a case, there exists the caveat that R ≠ H, as this leads to low yields and numerous side products. Palladium (II) catalyzed dehydrosilations to furnish enones have also been described. Such reactions are characteristically high yielding and regiospecific in unsymmetrical systems (Scheme 9b).[30]

Scheme 9. Enone Synthesis *via* Palladium Catalyzed Eliminations.

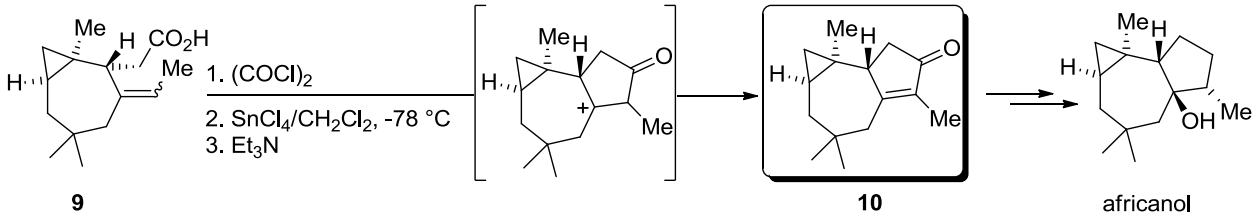


2.1.4 Acylation

There are three broadly-defined acylation routes to enones: (a) Friedel-Crafts acylations, (b) acylations of vinylsilanes, and (c) acylations of vinyl anions/equivalents. Route (a) has seen the greatest utility, owing to its longstanding establishment in organic synthesis.[31] A drawback of this reaction is that the Lewis acid catalyst is often unrecoverable, being destroyed during work-up. Recently, however, this has been circumvented with the use of heterogeneous catalysts, allowing this reaction to be a feasible one on larger scales.[32] In one example, the $SnCl_4$ catalyzed

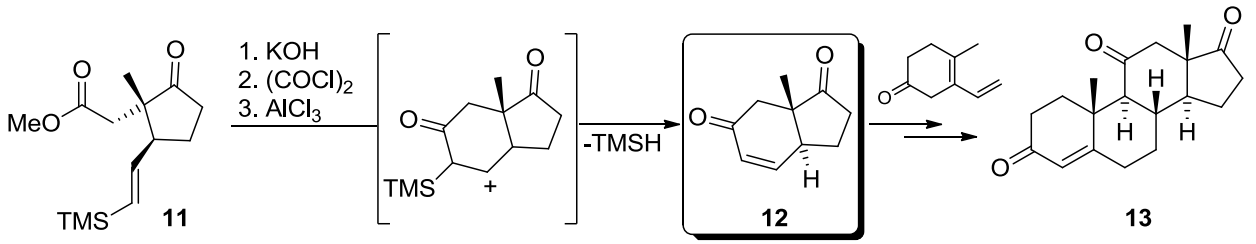
Friedel-Crafts acylation of olefinic acid **9** was successfully employed by Paquette and Ham to afford enone **10**. This species was elaborated further to the target natural product africanol (Scheme 10).[33]

Scheme 10. Enone Synthesis *via* Friedel-Crafts Acylation: Synthesis of Africanol.



In route (b), vinylsilanes are used in conjunction with acid chlorides, in what is also a Friedel-Crafts acylation. With this vinylsilane method, however, a high level of regiospecificity is obtained owing to the preferred *ipso* substitution *via* formation of the intermediate carbocation at the β position, which allows for maximum stabilization by silicon (the so called β effect). This acylation method has been used to prepare cyclic enones toward the total synthesis of the corticosteroid *trans*-7a-methylhydrind-4-ene-1,6-dione **13**. Here, key intermediate enone **12** was prepared using an intramolecular Friedel-Crafts acylation of vinylsilane **11** (Scheme 11).[34]

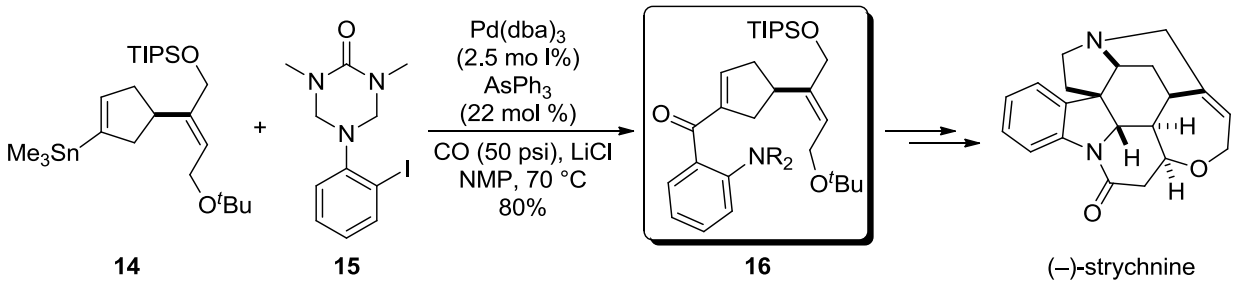
Scheme 11. Enone Synthesis *via* Intramolecular Friedel-Crafts Acylation of a Vinylsilane: Denmark's Synthesis of Corticosteroids.



Finally, route (c) involves the use of either a vinyl anion, or a suitable equivalent thereof. Such anions can be obtained quite easily through lithium-halogen exchange of vinyl iodides, for example.[35] Perhaps one of the most notable applications of these acylations is the Stille reaction. First reported in 1978, Stille built upon the previous synthetic work by Eaborn et al., Kosugi, and Migita, reporting milder conditions and improved yields.[36] In a particularly noteworthy example

of this method, Overman and co-workers utilized a carbonylative Stille cross-coupling in the first enantioselective total synthesis of (–)-strychnine.[37] The carbon skeleton of the main precursor for the key aza-Cope rearrangement/Mannich cyclization was assembled from vinylstannane **14** and *ortho*-aniline **15** to afford the aromatic enone **16** in 80% yield (Scheme 12).

Scheme 12. Enone Synthesis *via* Stille Carbonylative Cross-Coupling: Overman's Total Synthesis of (–)-Strychnine.



2.1.5 Other Synthetic Methods toward α,β-Unsaturated Ketones

In addition to the cases outlined above, a number of other common methods are employed toward enone synthesis, including carbonyl insertion,[38] ring expansions and contractions,[39] oxidation/reduction of aromatic compounds (e.g., Birch reduction[40]), pericyclic reactions such as retro Diels-Alder reactions,[41] and Baylis-Hillman reactions.[42]

2.2 Utility of α,β-Unsaturated Ketones in Organic Synthesis

There have been a number of notable examples of the α,β-unsaturated ketone moiety appearing in both target products and synthetic intermediates. A number of natural products contain this feature and many have been synthesized, including cyanthiwigin U,[43] (+)-cepharamine,[44] phorbol,[45] and prostaglandin A_2[46] (Figure 2). This gives us perhaps sufficient reason to investigate methods of enone synthesis, however their role as endgame targets does not represent the sole rationale for synthesis of this class of molecules.

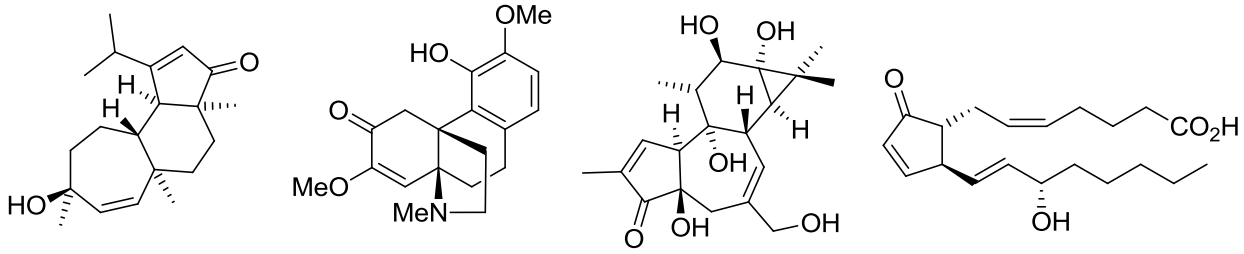


Figure 2. Selected Natural Products Containing an α,β-Unsaturated Ketone Moiety.

In addition to their presence in various natural product targets (e.g., those in Figure 2), enones also represent a well-studied, synthetically useful reagent class, suitable for a wide array of transformations. Indeed, each of the four atoms may be selectively exploited as a reactive centre. Particular attention has been paid to nucleophilic additions in a 1,2- or 1,4-manner, including catalytic and/or enantioselective examples (Figure 3). Further, a number of cycloadditions of the alkene with other π-systems have been described, with particular emphasis on formation of rings containing three to six members.

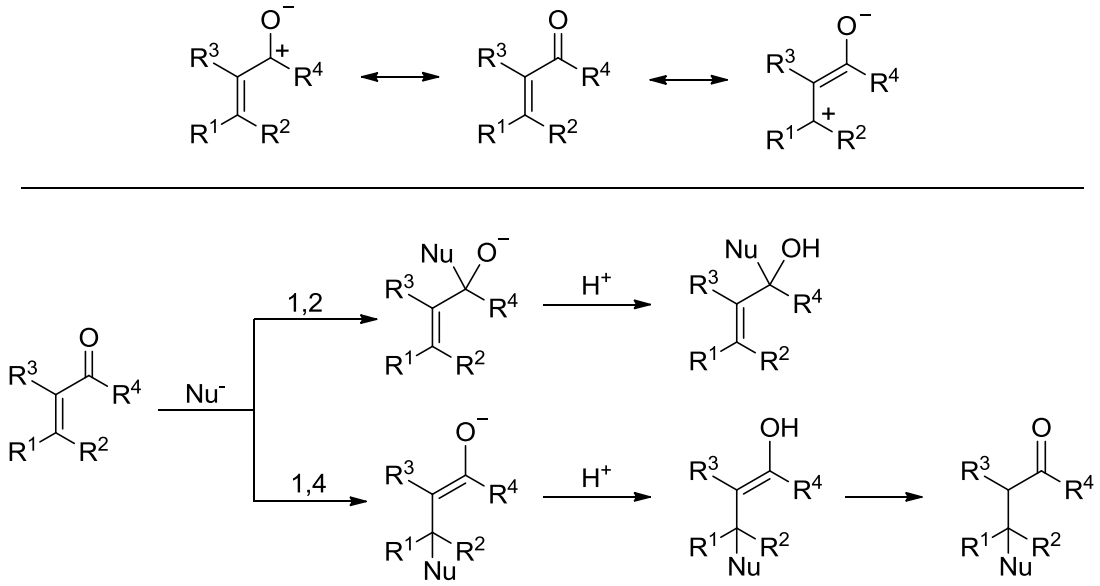


Figure 3. Reactivity Patterns in α,β-Unsaturated Carbonyl Species: 1,2- vs. 1,4-Addition of Nucleophiles.

2.2.1 1,2-Addition of Nucleophiles

Bond formation through 1,2-addition of nucleophiles is characterized primarily by Grignard-type addition to the carbonyl. However, the high reactivity of organomagnesium compounds often leads to a mixture of the 1,2- and 1,4-adduct, with the former dominating, which can limit their application. This family of reactions also includes alkyl- and aryllithium species, metal derivatives of allyl ethers, and other hard nucleophiles such as cyanide. In the latter case, the resulting cyanohydrins can be oxidized with magnesium (IV) oxide to the acyl cyanide (though only with enals); further reaction with methanol yields the α,β-unsaturated methyl ester, with the olefin geometry conserved. This method of obtaining unsaturated acids is synthetically useful, and preferable to direct oxidation of alkenals with silver oxide.[47] A slightly different application of 1,2-addition is addition of a secondary amine (e.g., pyrrolidine). Following dehydration of the initial amino alcohol, the formation of a linear dienamide results. *Trans*oid enones **17** yield linear dienamines **18** and **19**, whereas *cis*oid enones **20** give a mixture of linear **21** and so-called cross-conjugated dienamines **22** (Figure 4).[48]

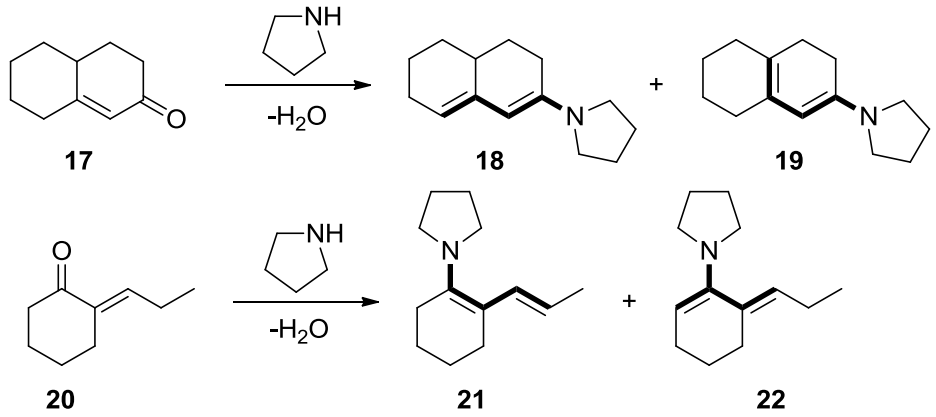
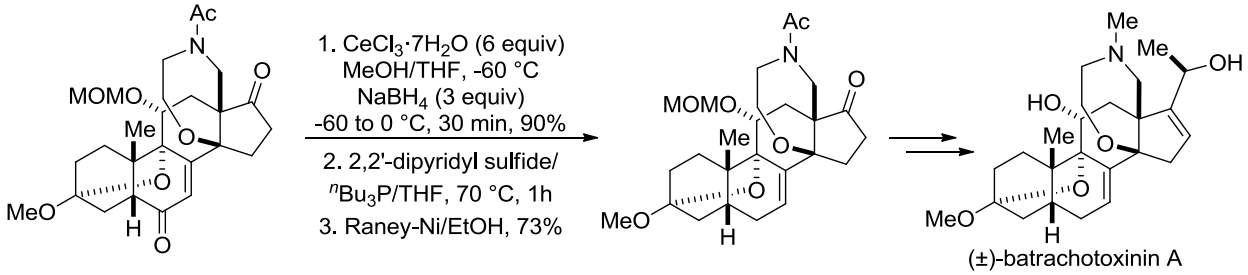


Figure 4. Schiff Base Formation between α,β-Unsaturated Ketones and Secondary Amines.

The transformation of enones to the corresponding allylic alcohols using a combination of cerium chloride and sodium borohydride (the so-called Luche reduction)[49] is a useful way to achieve the 1,2-reduction of such compounds. In fact, its breakthrough discovery constituted possibly the first reliable way to obtain the 1,2-reduction product in good yields, since alternative methods involving metal hydrides usually give a mixture of 1,2- and 1,4-reduction products.

Kishi and co-workers utilized a Luche reduction in their synthesis of (±)-batrachotoxinin A, followed by a thioetherification and Raney nickel reduction to effectively delete the carbonyl.[50]

Scheme 13. The Luche Reduction of Enones: Kishi's Synthesis of (±)-Batrachotoxinin A.



2.2.2 1,4-Additions of Nucleophiles (Conjugate Additions)

Owing to the large LUMO coefficient on the β-carbon of an enone, the necessary softness of a nucleophile required in order to react preferentially with the β-carbon has manifested itself in frequently observed conjugate additions with sulfur, selenium, halogen, and alkene nucleophiles.[51] Though the Michael addition has been known and explored fairly comprehensively, there has been a relatively recent surge in catalytic Michael additions to afford enantiopure products from enones. Particular note is given to this class of reactions, as catalytic methods for C–C bond formation are attractive to many chemists, and a number of pertinent protocols in recent years have been described.[52]

Popularized by Eric Jacobsen, aluminum salen complexes **23** have proven to be useful for catalyzed asymmetric conjugate addition reactions. These catalysts are amenable to enantioselective conjugate additions of electron deficient nitrile derivatives (including trisubstituted nitriles) to α,β-unsaturated imides (Figure 5).[53]

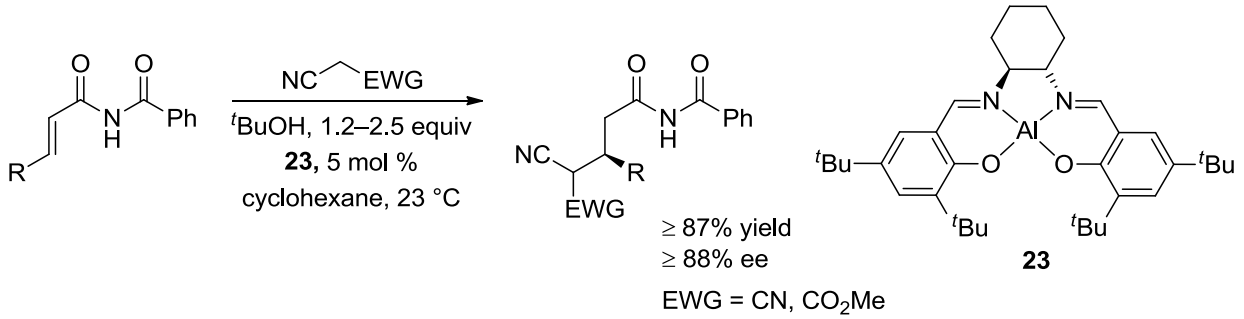
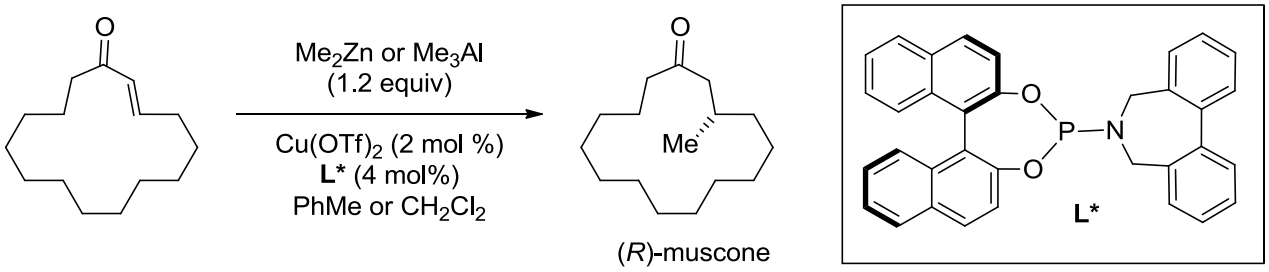


Figure 5. Aluminum Salen Catalyzed Conjugate Addition of Malononitrile and Methyl Cyanoacetate to α,β-Unsaturated Imides.

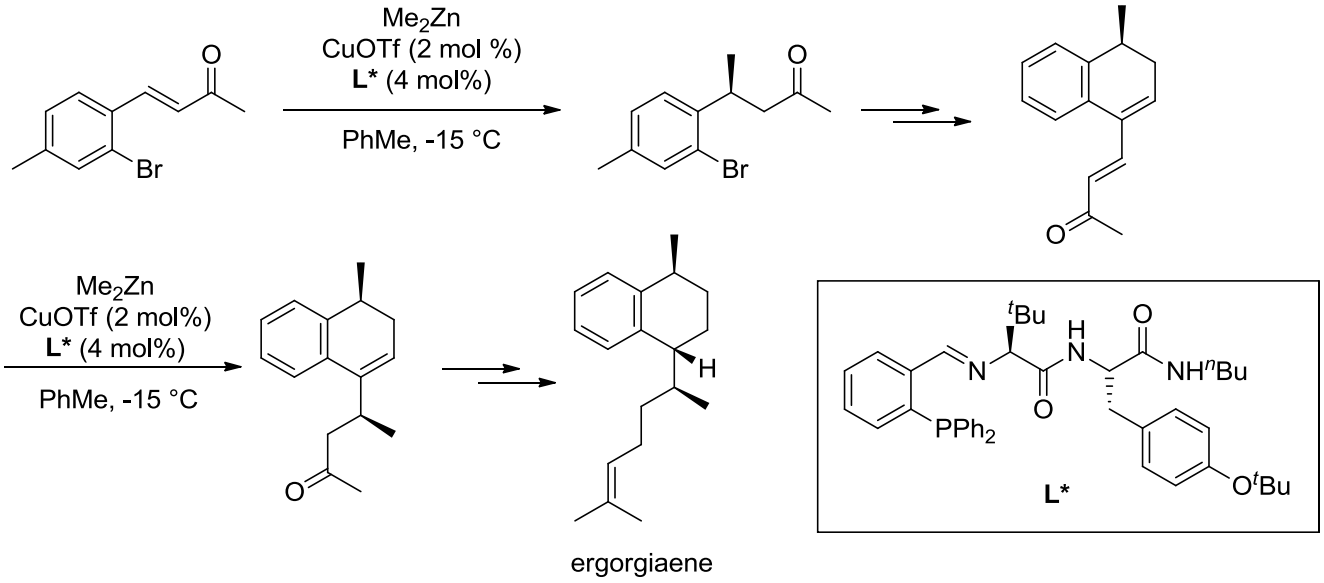
A popular trend in conjugate addition reactions over the last several decades has been the employment of organocopper species.[54] Such procedures, through carefully tuned reaction conditions and protocols, have truly vaulted the α,β-unsaturated carbonyl moiety to attractively high levels of synthetic utility more than any other reagent class. The methodology has its roots in the Grignard reaction, though the use of a copper catalyst affords a softer carbon nucleophile, reliably driving reactivity towards the β-carbon. Other organometallics may be utilized as well, notably those based on zinc[54b] and aluminum.[55] A particularly powerful mode of C–C bond formation is the rhodium-catalyzed 1,4-addition of arylboronic acids to activated alkenes (e.g., enones), developed by Miyaura and Hayashi.[56] This chemistry has since been extended to α,β-unsaturated esters, aldehydes, amides, phosphonates, sulfones, and nitro compounds.[57]

A frequent application of copper-catalyzed conjugate addition in industry is toward the synthesis of (*R*)-muscone, a commercially important fragrance molecule. A representative synthetic route is shown in Scheme 14, where cyclopentadecenone is methylated at the β-position, using alkylzinc or aluminum, with copper (II) triflate as a catalyst.[58] In another commercially viable synthetic route, Hoveyda and co-workers reported a five step synthesis of ergorgiaene, an inhibitor of *Mycobacterium tuberculosis*. This synthesis utilized two such asymmetric conjugate additions as key steps (Scheme 15).[59]

Scheme 14. Copper-Catalyzed Conjugate Methylation of Pentadecenone: Commercial Synthesis of *R*-Muscone.



Scheme 15. Hoveyda's Synthesis of Ergorgiaene *via* Two Copper-Catalyzed Conjugate Methylations.



Heteroatom nucleophiles may be used for conjugate additions as well. As mentioned previously, thiols react with enones to yield saturated ketones. This method has proven to be synthetically useful, for example in substituted pyridine synthesis (Figure 6a).[60] The Lewis acid catalyzed conjugate addition of allyltrimethylsilane to enones produces δ,ε-unsaturated enones, wherein the allyl group is transposed: the co-called Sakurai allylation (Figure 6b).[61] The highly reactive β-iodo ketone functionality may be furnished in good yields from trimethylsilyl iodide and various enones. The transformation takes place *via* a β-iodo silyl enol ether intermediate (Figure 6c).[62]

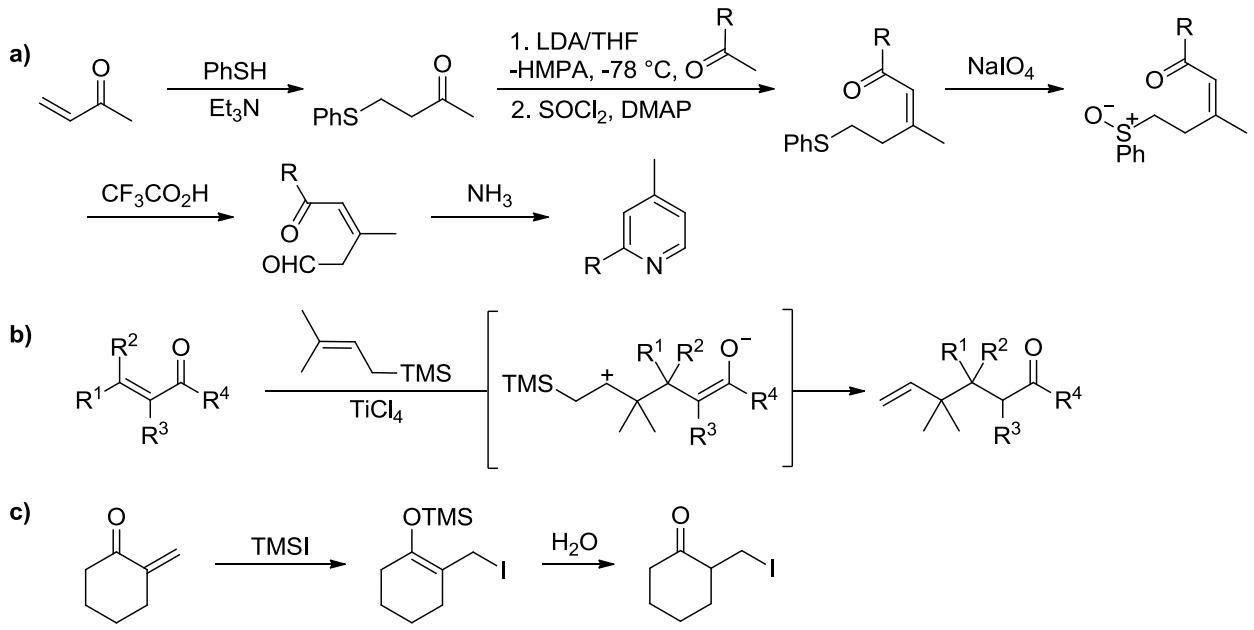
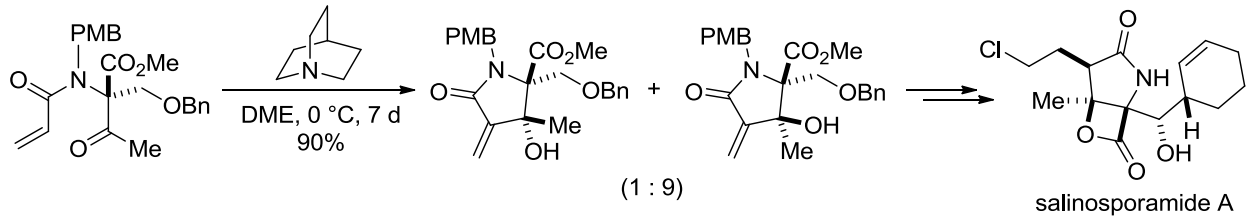


Figure 6. Conjugate Addition to Enones with Various Heteroatom Nucleophiles.

The Baylis–Hillman reaction involves the formation of a C–C single bond between the α-position of a conjugated carbonyl compound (e.g., an enone) and carbon electrophiles such as aldehydes and activated ketones in the presence of a suitable nucleophilic catalyst.[63] In Corey's synthesis of salinosporamide A, this reaction was applied to a ketoamide substrate to afford a mixture of diastereomers favoring the desired isomer (Scheme 16).[64]

Scheme 16. The Baylis-Hillman Reaction: Corey's Synthesis of Salinosporamide A.

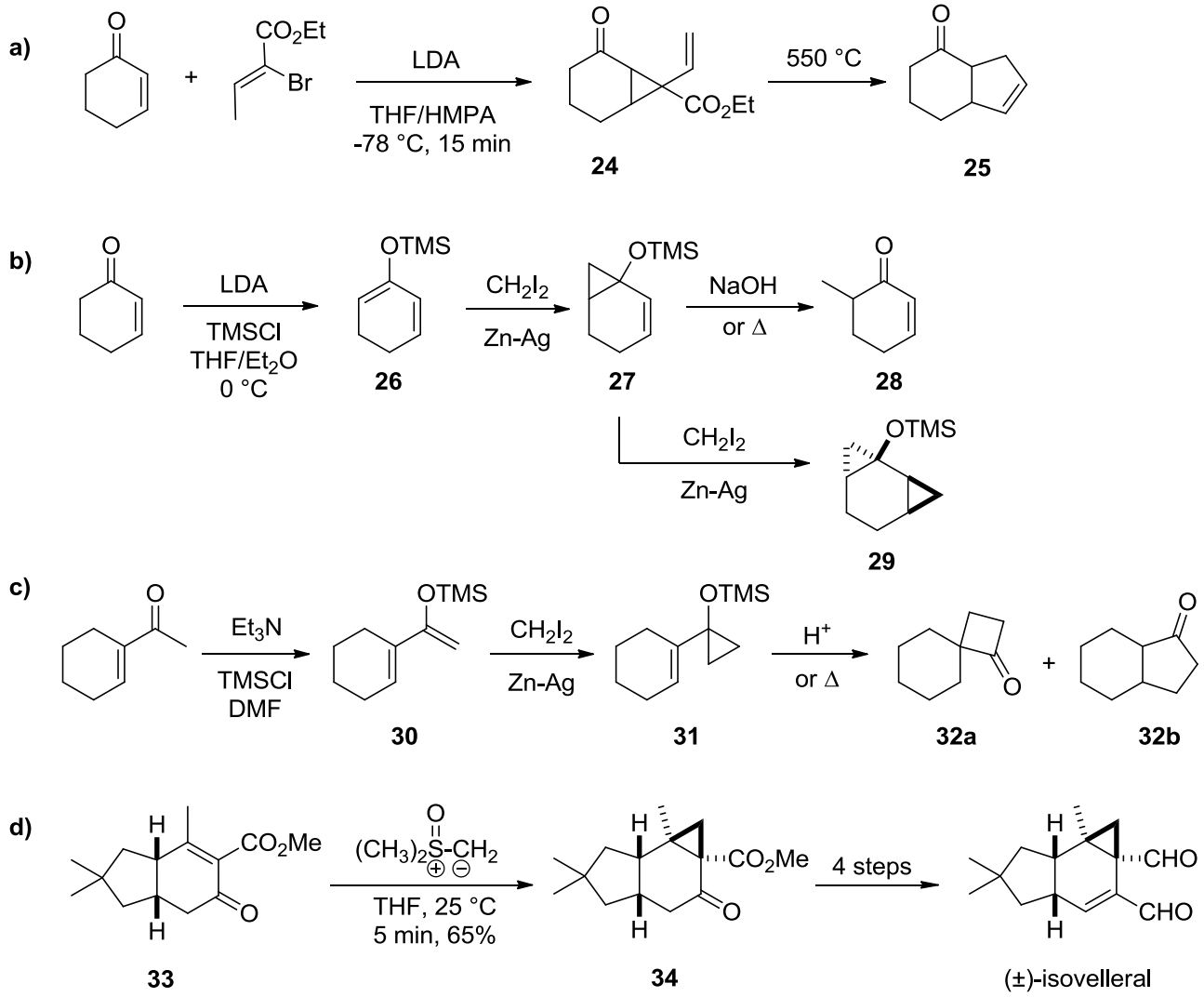


2.2.3 Cycloadditions to Enones

Enones can undergo cycloaddition reactions to form α-ketocarbocycles, with a variety of reagents, to afford a variety of ring sizes. Beginning for example with three-membered rings, enones may undergo epoxidation (e.g., in basic hydrogen peroxide)[65] or cyclopropanation (e.g.,

Corey-Chaykovsky cyclopropanation)[66] to form the appropriate three-membered fused ring. For example, in a reaction with ethyl α-bromocrotonoate and lithium diisopropylamide, cyclohexenone is transformed into vinyl cyclopropane **24**, which rearranges to the cyclopentene product **25** (Scheme 17a).[67a] In related chemistry, Conia and co-workers have shown that the enone can be converted to the conjugated silyl enol ether **26** and cyclopropanated at the resulting olefin under Simmons-Smith conditions to afford **27**. This useful product may be treated with base or heated to afford α-methyl cyclohexenone **28**,[67b] or further elaborated under the preceding conditions to afford the biscyclopropanated product **29** (Scheme 17b).[67c] This is especially interesting in comparison to the analogous *cis*oid compounds **30** (Scheme 17c), for which acid-catalyzed or thermally-promoted decomposition of the spiro cyclopropanation product **31** leads to the ring-expanded products **32**, rather than to a methylated product analogous to **28**.[67d] In the synthesis of (±)-isovelleral, Heathcock and co-workers utilized a Corey-Chaykovsy cyclopropanation of enone **33** using dimethylsulfoxonium methylide in THF. This is a noteworthy example as DMSO is the most common solvent for this reaction, though it was found to give inferior results in this case. The resulting cyclopropane **34** was further elaborated along a four step sequence in order to furnish the natural product (Scheme 17d).[67e]

Scheme 17. Formation of Three-Membered Rings With Enones.

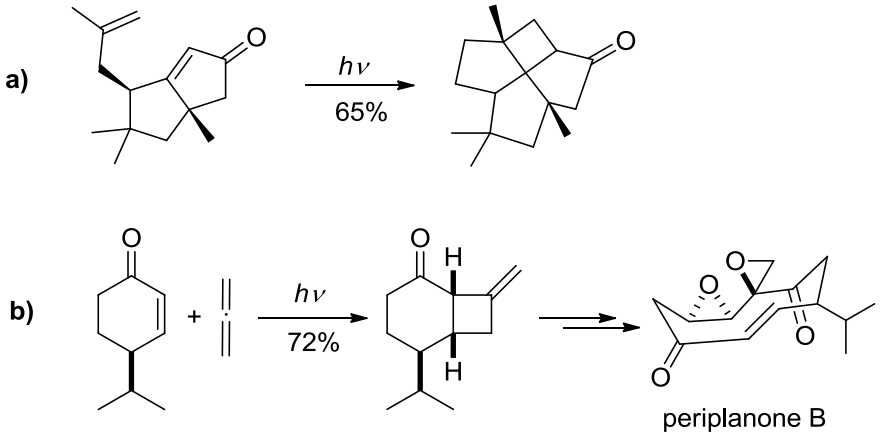


Though there have been a number of reported cases of cycloadditions to form four- and six-membered rings, the mechanisms thereof are composed largely of [2 + 2] cycloadditions[68] and Diels-Alder reactions,[69] respectively, two topics for which there is a wealth of information available. Under carefully controlled conditions in the latter, the enone may function as either the diene or the dienophile.

Photocatalyzed [2 + 2] cycloadditions of enones are useful in creating complex bridged polycyclic molecules. For example, Scheme 18a shows how Crimmins and co-workers were able to easily furnish the sterically congested fenestrane in high yield using an intramolecular [2 + 2] cycloaddition.[68a] Similarly, in their synthesis of the cockroach pheromone periplanone B,

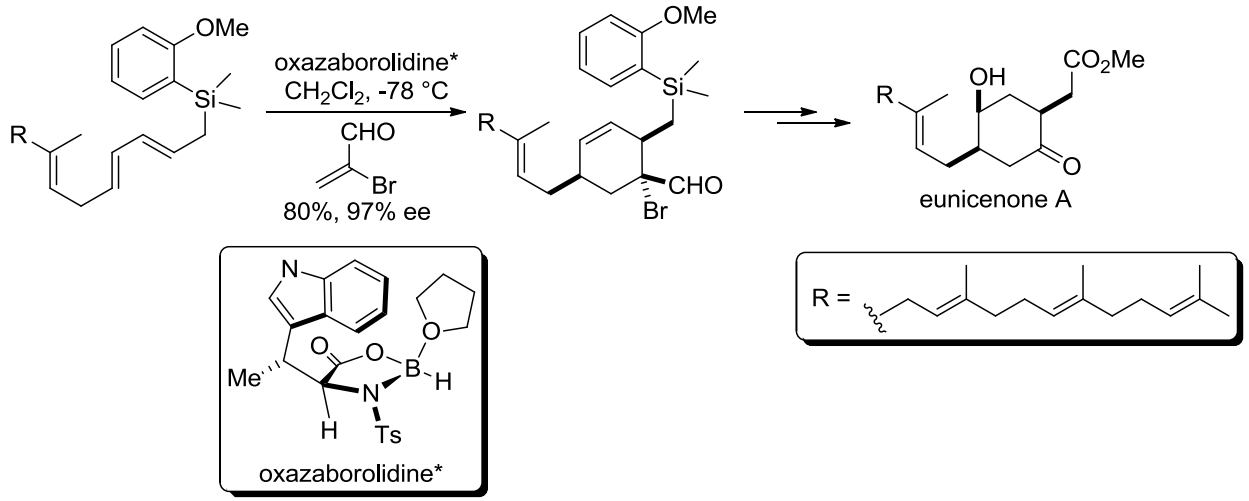
Schreiber and Santini utilized an intermolecular [2 + 2] cycloaddition between allene and 4-isopropyl-2-cyclohexe-1-none to build up the carbon skeleton *en route* to the target molecule (Scheme 18b).[68b]

Scheme 18. Intramolecular [2 + 2] Cycloadditions of Enones.



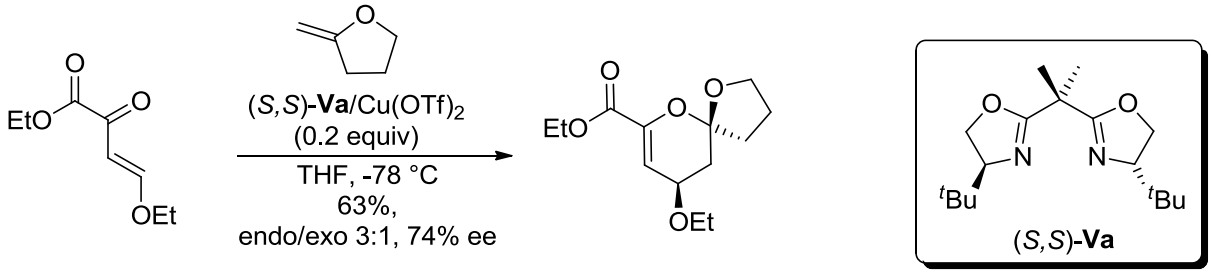
Enones and enals possess the ability to function as either dienophiles or as dienes in Diels–Alder reactions. For example, in their synthesis of eunicenone A, Corey and co-workers utilized an intermolecular chiral oxazaborolidone catalyzed Diels–Alder reaction with 2-bromoacrylaldehyde as the dienophile (Scheme 19).[70]

Scheme 19. Enals as Dienophiles in Diels–Alder Reactions: Corey's Synthesis of Eunicenone A.



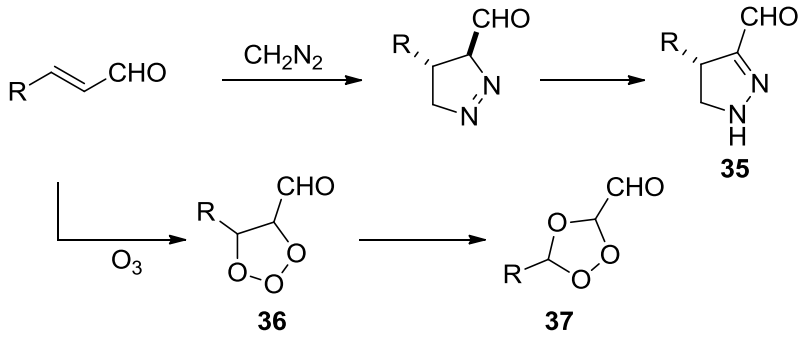
When α,β-unsaturated carbonyl compounds are involved in a hetero-Diels-Alder reaction as heterodienes, an inverse electron demand reaction takes place. For example, with very electron-rich dienophiles, α,β-unsaturated-α-ketoesters react under copper (II) catalysis with generally good yields and stereoselectivities (Scheme 20).[71]

Scheme 20. Enones as Dienes in the Hetero Diels–Alder Reaction



Synthesis of five-membered rings from enones has been less thoroughly investigated; in these cases the enone functions as a dipolarophile in 1,3-dipolar cycloaddition reactions. For example, addition of diazomethane to an alkenal yields pyrazolines **35**. As well, ozone undergoes facile cycloaddition with the olefin to give the corresponding trioxolan **36**, which rearranges to the ozonide (Scheme 21).

Scheme 21. Cycloaddition with Enones: Formation of Five-Membered Rings.



3 Allylation of Aldehydes Using Potassium Allyltrifluoroborate Salts

3.1 Introduction to Carbonyl Allylation

It seems particularly appropriate to begin a discussion on modern allylation chemistry with a glance backwards towards the beginnings of organic synthesis itself. Nearly every sophomore chemistry student today is familiar with famous Grignard reaction.[72] It, along with its predecessor, the Barbier reaction,[73] have become so intertwined with the history and milestones of organic synthesis over the last century, that it is still commonly utilized today. This Nobel Prize winning chemistry[74] laid the framework for C–C bond-forming transformations at a carbonyl center, a strategy still utilized in modern allylation chemistry.

This evolution was not to happen overnight. In fact it was not until the late 1970's that allylation chemistry became appreciated by the synthetic organic community at large. Prior to three papers on the subject of stereocontrolled allylic addition to carbonyls,[75] allylmetal compounds were studied primarily by organometallic chemists interested in the stereochemistry of such species. Reactions were carried out as well, but these were largely restricted to determining the S_E2 vs. S_E2' regioselectivity of the allylic unit in reactions with electrophiles (Figure 7).[76]

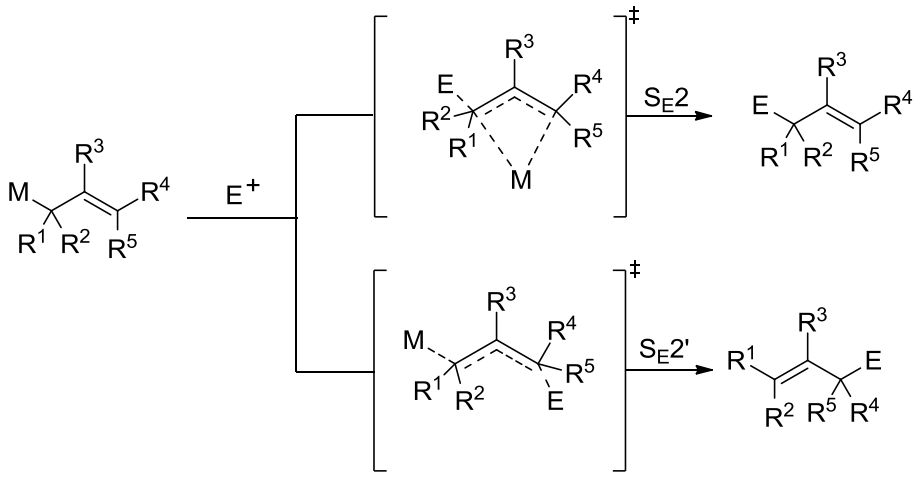


Figure 7. Variable Regioselectivity of Reactions of Allylmetal Reagents with Electrophiles.

Today, allylation and the related crotylation and prenylation reactions of aldehydes are widely used in organic synthesis for the assembly of homoallylic alcohols, which present themselves as

a particularly versatile class of synthetic intermediate.[77] A variety of organometallic reagents have been used to effect these transformations, including those based on Li, B, Mg, Al, Si, Ti, Cr, Zn, Zr, In, Sn, etc. The allylmetal–aldehyde addition has seen a major usage over the last two decades, particularly in efforts toward controlled assembly of open-chain systems bearing sequences of stereocentres. Indeed, in this application it has performed marvellously. Several attractive features about allylations are: (1) high degrees of both diastereo- and enantioselectivity are observed; (2) an extreme diversity of reagent reactivity can be achieved, tuned *via* judicious choice of metal; (3) the ability to assemble multiple contiguous stereocentres; and (4) the latent functionality in the homoallylic alcohol product makes the reaction a powerful tool in synthetic planning.[77] Furthermore, the reactions are mechanistically intriguing, with variable regio- and stereoselective outcomes attainable through judicious choice of reagent, substrate, and catalyst.

3.2 Allylation With Potassium Allyltrifluoroborate

3.2.1 Synthesis and Properties of Potassium Allyltrifluoroborate

Potassium organotrifluoroborate salts had received relatively little attention prior to the mid 1990's. Vedejs and co-workers became interested in aryltrifluoroborates as *in situ* precursors to boron difluoride Lewis acids, demonstrating the first expedient synthesis of these salts and their facile activation by fluoride scavengers.[78] Several years later, Omoto and Fujimoto released a computational study of allylation with various allylboron species, including allylboron difluoride.[79] This compound is analogous to the corresponding boronate esters and boronic acid (Figure 8a). In such compounds, electron donation from the oxygen atoms serves to deactivate the boron centre through π-donation, thereby lowering the electrophilicity of the compound and ultimately hindering reactivity towards aldehydes. Due to the large difference in electronegativities between boron and fluorine, it was postulated that electron delocalization between the two is suppressed, thereby localizing the unoccupied reactive orbital entirely on boron (Figure 8b). The implications of this are noteworthy: the allylation of aldehydes by allylboron difluoride is virtually barrierless. It was the combination of these two works that inspired Batey and co-workers to study potassium allyltrifluoroborate as a precursor for *in situ* conversion to allylboron difluoride and its reactivity towards aldehydes.

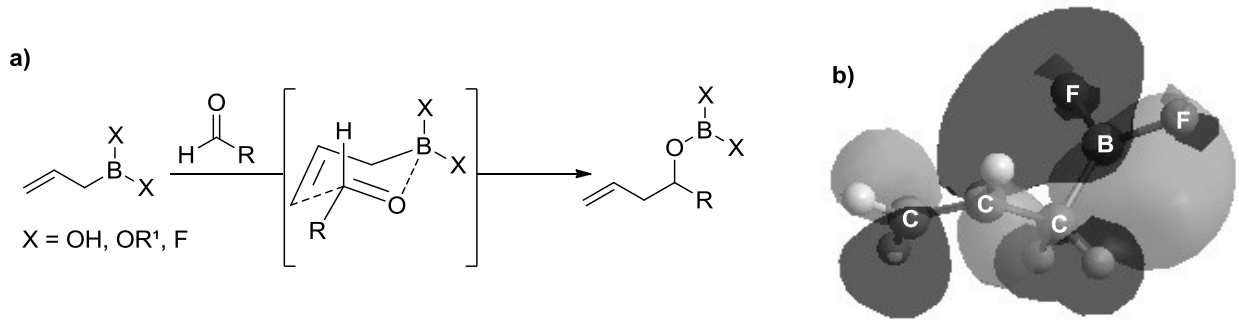
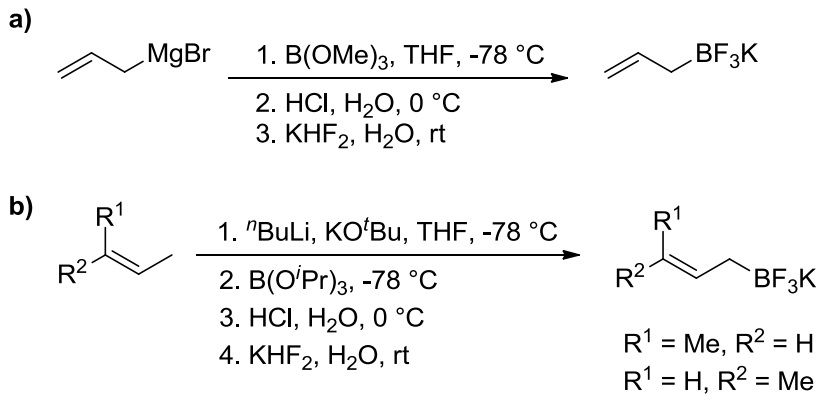


Figure 8. (a) General Allylation Reaction Pathway via Zimmerman-Traxler Transition State. (b) Large Boron-Centered LUMO of Allylboron Difluoride Responsible for Accepting Electron Delocalization from the Aldehyde.

There has been a long-standing interest in the Batey group regarding the preparation and application of potassium allyl- and crotyltrifluoroborate salts.[80] Prior to the group's seminal work in the area, there were two main classes of allyl- and crotylboron compounds, namely the respective dialkylboranes and boronates, but only one, allyl pinacol boronate, was commercially available. All other such boron compounds were necessarily prepared immediately before use, owing to their inherent instabilities toward air and/or moisture. Potassium allyltrifluoroborates on the other hand are easily prepared *via* the boronic acid, and can be stored for extended periods of time at room temperature in plastic bottles (Scheme 22a). These initial studies were later elaborated upon, reporting both *E* and *Z* crotylations,[80] as well as prenylation[81] of aldehydes and ketones with the corresponding potassium trifluoroborates. These analogous boron reagents are prepared in a similar fashion to the allyl species (Scheme 22b).

Scheme 22. (a) Synthesis of Potassium Allyltrifluoroborate. (b) Synthesis of *E*- and *Z*-Potassium Crotyltrifluoroborate.



3.2.2 Reactions of Potassium Allyltrifluoroborate

The reactions of allyl- and crotyltrifluoroborates with aldehydes and ketones have proven to be remarkably successful in terms of chemoselectivity and practical facility. A number of publications by the Batey group outline this quite well, synthesizing homoallylic alcohol products in yields ≥ 90% in as little as 10 minutes. In the case of crotyl reagents, diastereomeric ratios are on the order of 95:5, cumulatively providing one of the most operationally simple approaches to the allylation and crotylation of aldehydes.[80f] A number of reaction catalysts have been reported, including $BF_3{\cdot}OEt_2$,[80a,b] indium metal,[80g] phase-transfer catalysts,[80d] and montmorillonite K10.[80f] The latter is a smectite clay with both Brønsted and Lewis acidic character. It has previously seen use as a catalyst in organic reactions.[82] In each case, the catalyst presumably serves to convert the tetravalent borate species to trivalent allyldifluoroborane in order to invoke the reactivity outlined in Figure 8a.

In addition to the inherent advantages of heterogeneous catalysis (e.g., facile delivery and removal of catalyst), the montmorillonite K10 method boasts certain advantages over those using $BF_3{\cdot}OEt_2$. First, allylation using $BF_3{\cdot}OEt_2$ requires anhydrous and inert atmosphere manipulation, and often cryogenic temperatures (-78 °C). Second, although $BF_3{\cdot}OEt_2$ can be used catalytically in these reactions, this requires extended reaction times (3−6 h). Stoichiometric quantities of $BF_3{\cdot}OEt_2$ are required in order to achieve full conversion in 15 minutes, albeit at the low temperatures stated above. The montmorillonite-catalyzed procedure can be performed under ambient conditions under an atmosphere of air. In fact water is required as an additive in order

to achieve proper swelling of the clay necessary for optimal catalytic activity. Furthermore, montmorillonite K10 is quite inexpensive ($57.40 / kg from Sigma Aldrich) and has no documented tendency to degrade over time at room temperature, quite unlike $BF_3 \cdot OEt_2$.

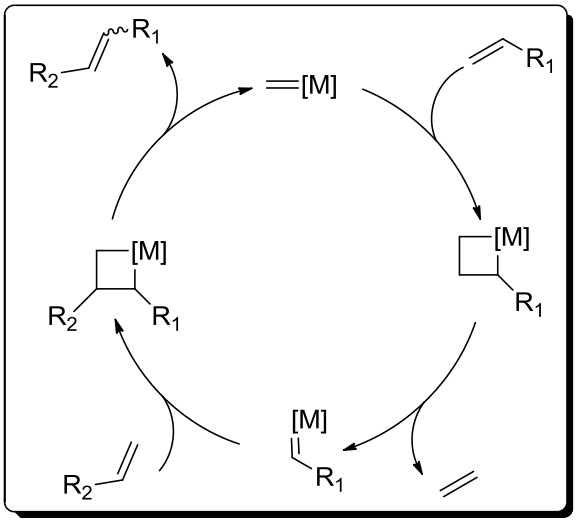
With such an impressive array of reasons to use it, this montmorillonite catalyzed method of aldehyde allylation was seen as particularly interesting and certainly worthy of further investigation for use in organic synthesis. The homoallylic alcohol products resulting from such aldehyde allylations are useful synthetic intermediates particularly in molecules containing additional olefins, which may then undergo ring closing metathesis operations to afford various carbocycles (*vide infra*).

4 Ring-Closing Olefin Metathesis

4.1 Introduction to Olefin Metathesis

Seminal work in the field of metathesis began in the mid-1950's, when DuPont chemists Anderson and Merckling reported the first carbon-carbon double-bond rearrangement in the titanium-catalyzed polymerization of norbornene.[83] Several years thereafter the disproportionation of olefins to homologues of longer and shorter chain length was reported by Banks and Bailey.[84] Since then the field has exploded, and olefin metathesis now serves as an important tool in synthetic organic chemistry. Although many details the olefin mechanism remain speculative, the generally accepted mechanism for the process is as outlined by Chauvin and Hérisson in 1970, involving metallocyclobutane intermediates generated by the coordination of olefin and metal alkylidene *via* a series of [2 + 2}-cycloaddition and cycloreversion steps (Scheme 23).[85] The reversibility of the individual steps of this reaction necessarily generates an equilibrium mixture of olefins,[86] and it is thus imperative to shift the equilibrium to the right to make this reaction useful.

Scheme 23. Catalytic Cycle of Olefin Metathesis.



Common metathesis reaction types include cross-metathesis (CM), ring-closing metathesis (RCM), and ring-opening metathesis (particularly ring-opening metathesis polymerization, ROMP). The latter is driven by strain release, which contributes greatly to the irreversibility of

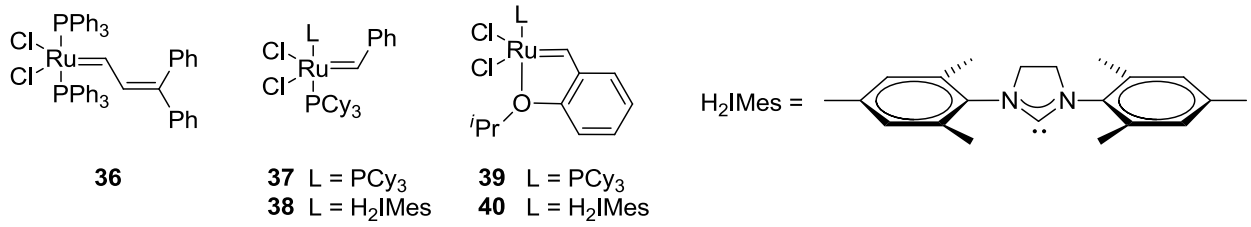
this reaction type. Indeed, ROMP was among the earliest commercial applications of olefin metathesis.[87] RCM also benefits from an equilibrium shift to the right, though it is mostly an entropic one as one molecule of substrate affords two molecules of product. The effect is further reinforced by the inherent volatility of the small molecules released from this process, which are often gaseous. These reactions are therefore practically irreversible, and can proceed to completion.[88] CM, on the other hand, is a more challenging process as it lacks both the entropic and thermodynamic driving forces, which often lead to poor yields of the desired cross-product. For such reasons it remains an under-exploited application of metathesis.[89]

A number of transition metal metathesis catalysts have been developed as the field has grown. Though the identity of the metal still varies to some degree today, some have shown greater activity and practicality than others; namely ruthenium and molybdenum. Before skipping too far ahead in the story of metathesis, it seems perhaps more appropriate to investigate the earliest such catalysts, as they have indeed paved the way for modern species.

Transition-metal halides and main-group metal alkyl co-catalysts served as the foundation to modern metathesis catalysts. Representative examples include $WCl_6/BuSn_4$, $WCl_6/EtAlCl_2$, and MoO_3/SiO_2.[89] Even to the experienced organic chemist, these catalytic systems may well seem daunting, or at the very least inconvenient to perform. Indeed these species saw limited utility in synthesis due the harsh conditions and prolonged initiation periods they required. To make matters worse, propagation processes were poorly controlled resulting in non-quantitative and non-uniform products. Improvements were seen beginning in the late 1970's when the first single-component catalysts were introduced based on tantalum,[90] tungsten,[91] and titanium.[92] Drawbacks to these systems included limited functional group tolerance and sensitivity to oxygen and moisture, albeit with very high catalytic activities. Oxophilicity and related functional group tolerance issues were resolved with the use of ruthenium-based catalysts, though not without a considerable amount of time and research invested.

4.2 Grubbs' Ruthenium Metathesis Catalysts

The first dramatic step towards a practical, reliable, and versatile metathesis catalyst came with the development of ruthenium-based species in the late 1980's.[93] Granted, ROMP catalyzed with $RuCl_3(H_2O)_n$ had been known since the early 1960's, however this ill-defined process stood alone as the sole application of the metal in metathesis for some 20 years.[94] In stark contrast to its predecessors, ruthenium was shown to be incredibly tolerant towards oxygen, moisture, and many functional groups even in early, ill-defined systems. An important advance in understanding the metathesis process came during this time when the first hypothesis was presented suggesting that the active species was in fact a ruthenium-alkylidene.[95] The first well-defined metathesis-active ruthenium alkylidene complex **36** was thus achieved in 1992 (Figure 9) though it displayed a relatively low reactivity and only effected the ROMP of severely strained olefins.[96] Nevertheless, the 1990's saw the rapid development of ruthenium-alkylidene catalysts with increased robustness and functional group tolerance.



36 **37** L = PCy_3 **38** L = H_2IMes **39** L = PCy_3 **40** L = H_2IMes

Figure 9. Modern Ruthenium-Alkylidene Based Olefin Metathesis Catalysts.

Ruthenium-based metathesis catalysts (L_2X_2Ru=CHR) are often categorized as one of two so-called "generations". In the first-generation catalysts, both neutral ligands (L) are phosphines, while in the second-generation species, one of the neutral ligands is a heterocyclic carbene. Robert H. Grubbs first described his namesake first-generation catalyst **37** (Figure 9) in 1995, reporting an initiation rate 1000 times greater than that of **36** in the ROMP of norbornene.[97] Replacement of one of the phosphine ligands with the bulky *N*-heterocyclic carbene ligand H_2IMes yields catalyst **38** (Figure 9), commonly known as Grubbs' second-generation catalyst. The net effect of this ligand substitution is improved catalytic activity as well as air- and moisture-stability, while maintaining the high functional group tolerance and thermal stability exhibited by **37**.[98] This improvement is ascribed to the affinity of the NHC-substituted ruthenium

center to π-acidic olefins over σ-donating phosphines.[99] More recently-developed ruthenium catalysts **39** and **40**, the so-called Hoveyda–Grubbs catalysts, have abandoned the second phosphine in favor of a bidentate alkylidine complex, which has been shown to increase thermal stability.[100] It is for the aforementioned reasons that catalyst **38** was utilized so heavily in the work described here (*vide infra*).

4.3 Metathesis in Total Synthesis and Industry

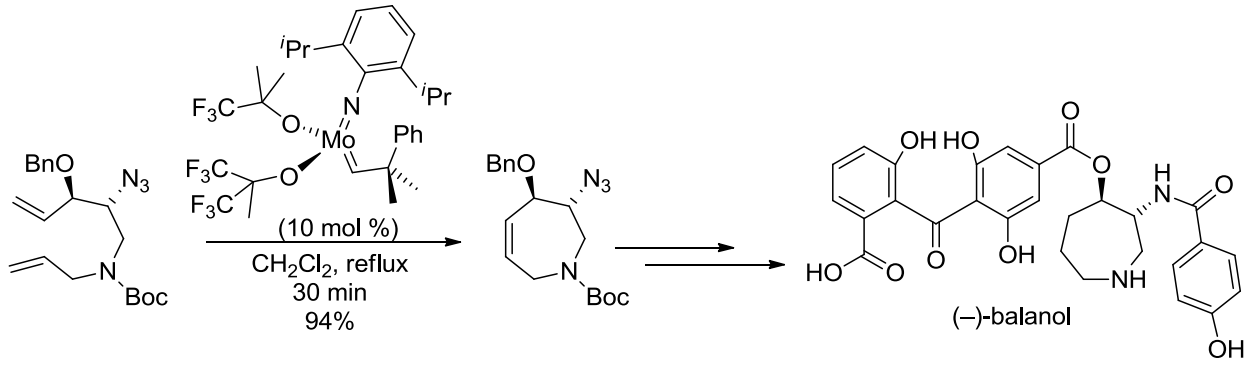
The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock for the development of the metathesis method in organic synthesis. It can perhaps go without saying that such a prize is awarded only to the most deserving contributions to science, a distinction that olefin metathesis very appropriately fulfills. That it has launched itself in only a few decades from a curious polymerization pathway to a powerhouse of a synthetic tool for the assembly of olefins, particularly in RCM and ROMP applications, is certainly remarkable. Today, metathesis is being used more than ever before owing greatly to the breakthrough in research since the 1990's in particular.

Richard R. Schrock is credited with developing the first useful well-defined metathesis catalysts. Such research is marked with the early advent of tantalum-alkylidene complexes. Schrock and co-workers reported in 1980 a tantalum-alkylidene species [Ta(=CHC$(CH_3)_3$)Cl(PMe_3)(O-C$(CH_3)_3)_2$], which they used to catalyze the metathesis of *cis*-2-pentene. This was notable at the time, since it represented the first example of such a tantalum species to do so, which the researchers attributed to the alkoxide ligands.[101] The work later expanded to cover molybdenum- and tungsten-alkylidene species of the general formula [M(=CHMe_2Ph)(=N-Ar)(OR_2)], where R is a bulky group (e.g., ^{t}Bu, $(CF_3)_2(CH_3)$C, $(CH_3)_2(C_6H_5)$C, etc.). These species are among the most active metathesis catalysts known, and such molybdenum species have been made commercially available.[102]

Grubbs and Schrock catalysts have provided chemists with new synthetic opportunities since their introduction. A number of syntheses have utilized a RCM or CM operation as a key step, and often with high degrees of success. For example, in his formal synthesis of (–)-balanol,

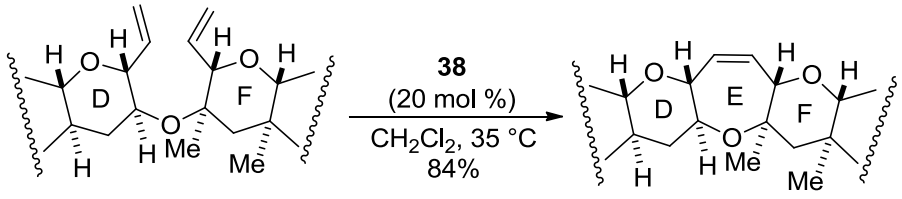
Fürstner formed the seven-membered amine using a molybdenum-based Schrock catalyst, achieving a 94 % yield after 30 minutes in refluxing dichloromethane (Scheme 24).[103]

Scheme 24. Fürstner's Use of Mo-Catalyzed RCM in the Synthesis of (–)-Balanol.



Large ladder-like polycyclic ethers characterized by such species as brevetoxin B have been an attractive synthetic target and subject of study, owing to their uniquely potent biological activities. In his synthesis of gambierol, Yamamoto utilized Grubbs' second-generation catalyst **38** to close the E ring through a RCM approach (Scheme 25).[104]

Scheme 25. Yamamoto's Use of Grubbs' Second-Generation Catalyst in the Synthesis of Gambierol.

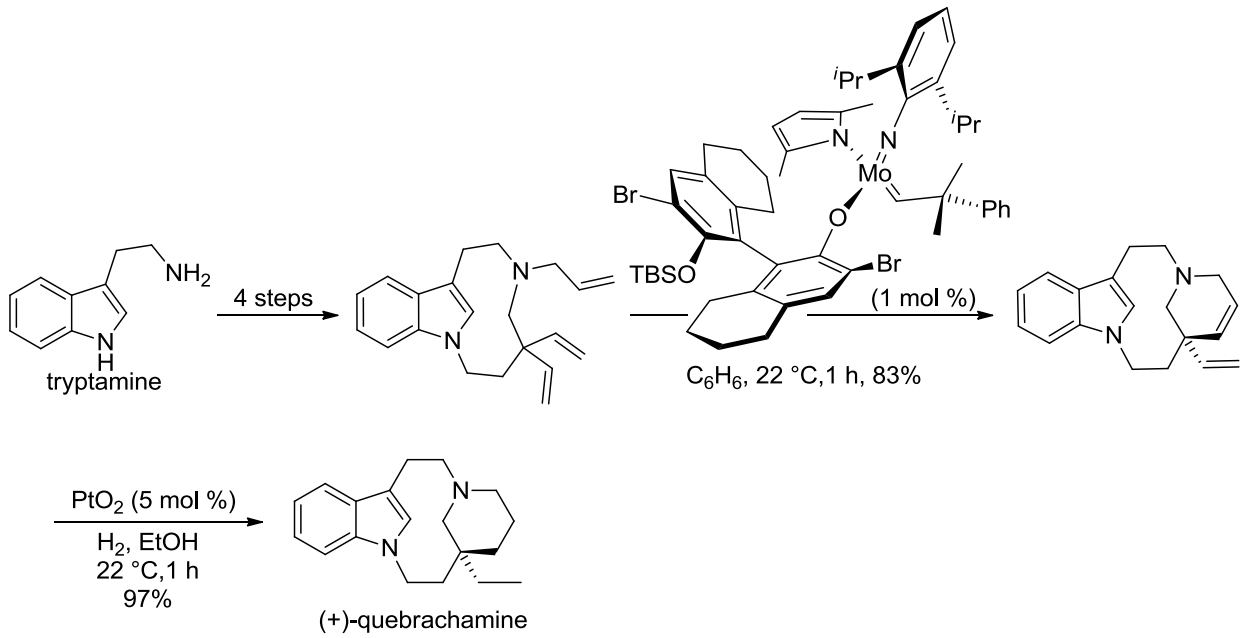


The utility of RCM in total synthesis is not limited to the above examples; scores of other total synthesis have utilized RCM catalysis with both molybdenum- and ruthenium-alkylidene species sharing the spotlight. However, despite the pioneer status and high activity of Schrock-type molybdenum catalysts, the sheer practicality of Grubbs-type ruthenium catalysts has established these as the go-to catalysts typical for RCM applications.[105]

In a beautiful example of the powerful potential RCM holds in total synthesis, Hoveyda and co-workers utilized a stereogenic-at-Mo catalyst to effect an enantioselective ring-closing operation

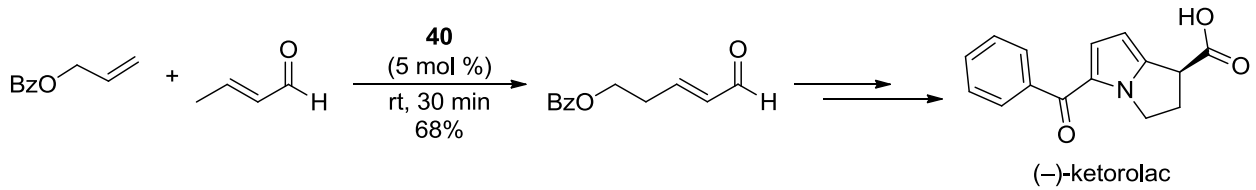
in the synthesis of (+)-quebrachamine.[106] The RCM substrate was synthesized in four steps from tryptamine, and then treated with the molybdenum metathesis catalyst in order to afford the dehydro- precursor to the natural product, which upon catalytic hydrogenation furnished (+)-quebrachamine in excellent yield (Scheme 26).

Scheme 26. Hoveyda's Use of a Stereogenic-at-Molybdenum Catalyst in the Synthesis of (+)-Quebrachamine.



Olefin metathesis has found utility in industrial-scale applications as well. A number of agrochemical and pharmaceutical compounds feature cross-metathesis reactions in their syntheses. Low catalyst loadings and the ability for these reactions to be run neat makes such synthetic routes attractive for commercial chemical suppliers. Scheme 27 shows a commercial synthesis of (–)-ketorolac, an NSAID commonly administered as a racemate. The (+)-enantiomer is associated with gastrointestinal side effects, making the enantiopure synthesis of the drug practical both clinically and economically.[107]

Scheme 27. Commercial Synthesis of (–)-Ketorolac *via* Hoveyda–Grubbs Catalyzed Olefin Cross-Metathesis.



First commercialized in 1977 by Royal Dutch Shell, the Shell higher olefins process (SHOP) is a three stage method for the industrial synthesis of higher linear olefins from ethylene. First, the oligomerization of the gas at 90–100 °C and 100–110 bar in a polar solvent (e.g., 1,4-butanediol) using a nickel phosphine catalyst gives a mixture of linear even-numbered α-olefins ranging from C_4 to C_{40}. Solvent choice is important, as the resulting higher alkenes must be immiscible with the solvent such that product and catalyst phases may be separated. Product α-alkenes of chain length C_6 to C_{18} are collected *via* distillation and either separated into individual compounds, used as co-monomer in polyethylene production, or converted into synthetic lubricants, plasticizers, detergents, etc. The second step of the process is potassium-catalyzed isomerization of the $< C_6$ and $> C_{18}$ olefins to afford a mixture of internal alkene products. Finally, the third stage of SHOP is the molybdenum-catalyzed cross metathesis of these internal alkene products to give a statistical distribution of odd- and even-numbered internal olefins, with a 10–15% yield of the desired linear C_{11} to C_{14} internal alkenes per pass, with the remainder again subjected to isomerization. Shell Chemicals' total worldwide production capacity of linear alpha and internal olefins per year is 1,190,000 t.[108]

These examples, along with many others in academia and industry, illustrate the versatility and powerful utility of olefin metathesis processes. It would appear that this field of chemistry is still growing, with scientists still applying RCM, CM, and ROMP with great success and creativity to afford products both synthetically interesting and globally important.

Chapter 2
Results and Discussion

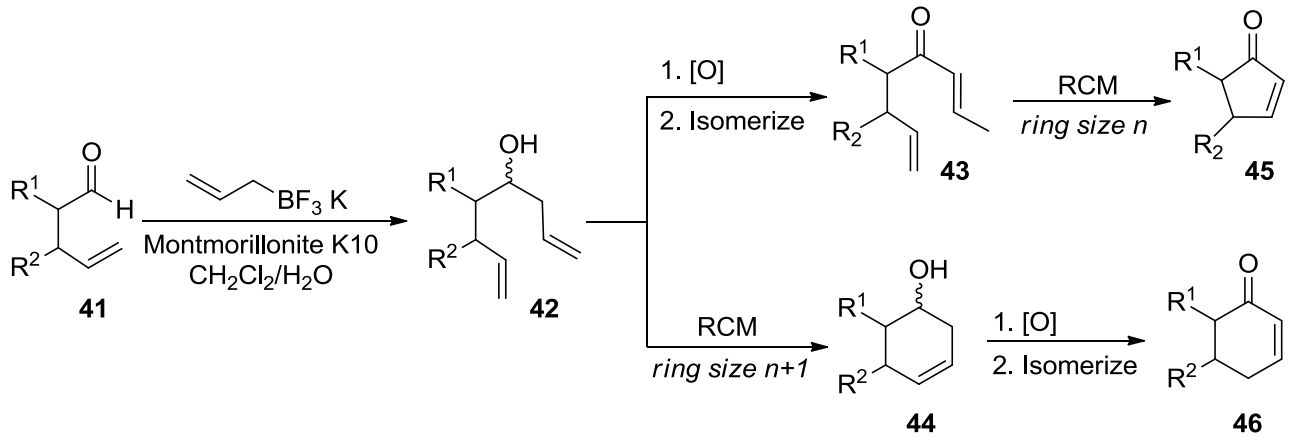
5 Synthetic Strategy

5.1 Project Genesis and Approach

In 2009, a convenient method for the allylation and crotylation of aldehydes and ketones using air- and moisture-stable potassium allyl and crotyltrifluoroborate salts was reported by Batey and co-workers. The reactions is done under mild conditions, at room temperature, under air, catalyzed by montmorillonite K10, and have proven to be scalable, providing homoallylic alcohols in high yields (95%) with short reaction times (15 min).[80f] As an extension of this methodology, and with particular focus on embracing the practicality with which it can be executed (i.e., scalability, facility, robustness, selectivity, etc.), focus turned toward exploring substrate scope. Since the conditions are mild and selective, the methodology may accommodate a wide variety of substrates, with many functionalities tolerated. Since ring-closing olefin metathesis has proven to be quite powerful in organic synthesis (see Section 4.3), it seemed a very interesting avenue to explore. In an albeit more idiomatic manner, one may note the appropriateness with pairing these two methodologies, since both are incredibly simple, reliable, and powerful. To this end, the divergent pathway outlined in Scheme 28 illustrates the methodological outline of this work, with a great deal of variability permitted in the R groups of the substrates, and certainly a great deal more yet to be explored. Though this outline describes five- and six-membered enone targets, any pair of cyclic enones with a relationship of n / (n+1) between the numbers of atoms in each respective ring may be accessible with this method.

The approach is simple but effective: From an unsaturated aldehyde **41**, the homoallylic alcohol **42** can be furnished using montmorillonite-catalyzed allylation chemistry, which functions as a common intermediate. This represents the branching divergence point, whereupon oxidation of the alcohol to the ketone is followed by base-induced isomerization of the double bond into conjugation with the carbonyl (**43**). Subjection of this enone to ring-closing olefin metathesis conditions affords a cyclic α,β-unsaturated ketone **45**. On the other hand, if the RCM and oxidation/isomerization steps are done in reverse order, a cyclic α,β-unsaturated ketone of ring size one member greater than the former is produced (**46**).

Scheme 28. Divergent Synthetic Strategy toward Cyclic α,β-Unsaturated Ketones from a Common Homoallylic Alcohol Intermediate



This divergent synthetic strategy was first explored by a previous post-doctoral fellow in the Batey group, Dr. Alejandro Castro, who applied it to γ,δ-unsaturated aldehydes to yield synthetically useful homoallylic alcohols, which were subsequently used to access the corresponding 5- or 6-membered cyclic enones through sequence of oxidation/isomerization and ring-closing metathesis reactions. The fruits of his labour are summarized in Figure 10.

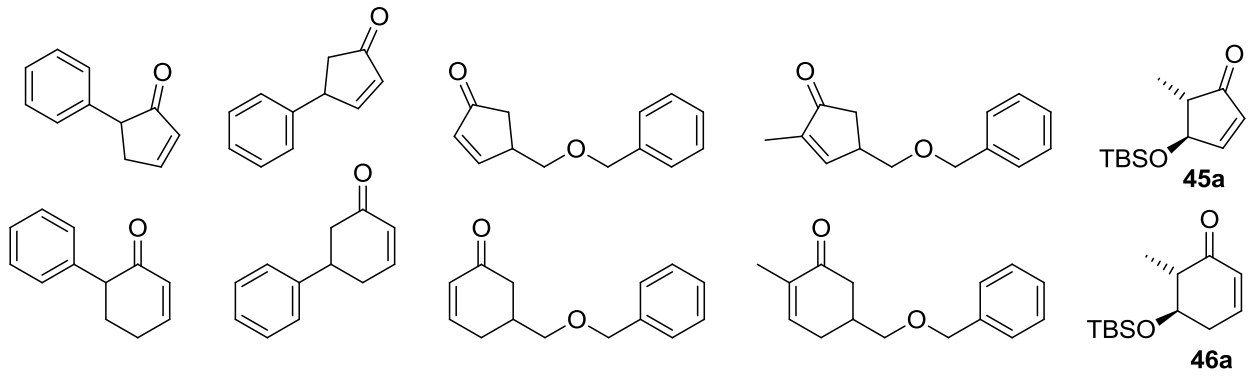


Figure 10. Cyclic Enone Products Synthesized by Dr. Alejandro Castro.

To further the scope of this approach, it was desired that it should be applied to more densely-functionalized substrates, namely toward fused-ring, heterocyclic, and/or enantiopure products, in order to demonstrate maximum utility. Furthermore, investigation of cyclic enones of ring size greater than six members was undertaken. As an added application, this work has potential utility

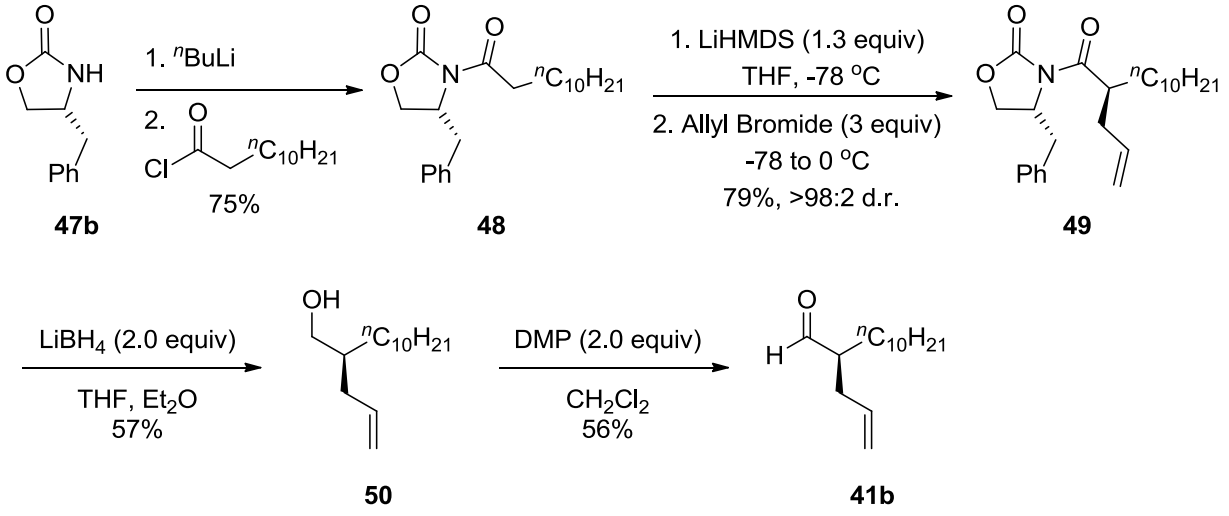
in an expedient route to members of the stemona alkaloid family. However, due to time restraints this has yet to be undertaken.[109]

Though they represented the proof-of-concept necessary to this project, the pioneering enone products shown in Figure 10 lack the aforementioned qualities, save for a pair of disubstituted enone products **45a** and **46a** which were synthesized in an enantiopure fashion. These served as the starting point for the work described here, using an Evans chiral auxiliary-based approach to synthesize the necessary enantiopure starting materials.[110]

5.2 Routes Toward Unsaturated Aldehyde Precursors to Homoallyllic Alcohols

In contrast to the preceding examples (Figure 10), the project described herein began with consideration of a long lipophilic chain in the α-position of the final enone. In order to install this, a chiral γ,δ-unsaturated aldehyde was synthesized, beginning from commercially available lauroyl chloride and a chiral oxazolidinone auxiliary **47** (Scheme 29).[111] Assembly of the *N*-acyl oxazolidinone **48** followed by installation of the allyl group by way of standard lithium enolate attack on to allyl bromide furnished **49** smoothly. Removal of the chiral auxiliary was accomplished with lithium borohydride in THF/ether, yielding alcohol **50**, which was oxidized to the corresponding aldehyde **41b**. Though certain isolated yields were low in this sequence, the reactions were easily performed and products easily purified on scales appropriately large for this preliminary stage such that no further starting material was required for synthesizing this target.

Scheme 29. Enantiopure Synthesis of Lipophilic Unsaturated Aldehyde from Lauroyl Chloride Using a Chiral Oxazolidinone Auxiliary.



A similar approach[112] was taken to aldehyde **41c** wherein the (*S*)-enantiomer **47c** of the aforementioned chiral auxiliary was acylated with 3-phenylpropanoyl chloride (easily prepared from the corresponding carboxylic acid by stirring with oxalyl chloride in dichloromethane for

three hours).[113] Cleavage of the oxazolidinone was accomplished with lithium aluminum hydride in ether, and the resulting alcohol **53** was oxidized to the aldehyde with DMP (Scheme 30).[114]

Scheme 30. Enantiopure Synthesis of α-Benzyl Pent-4-enal Using a Chiral Oxazolidinone Auxiliary.

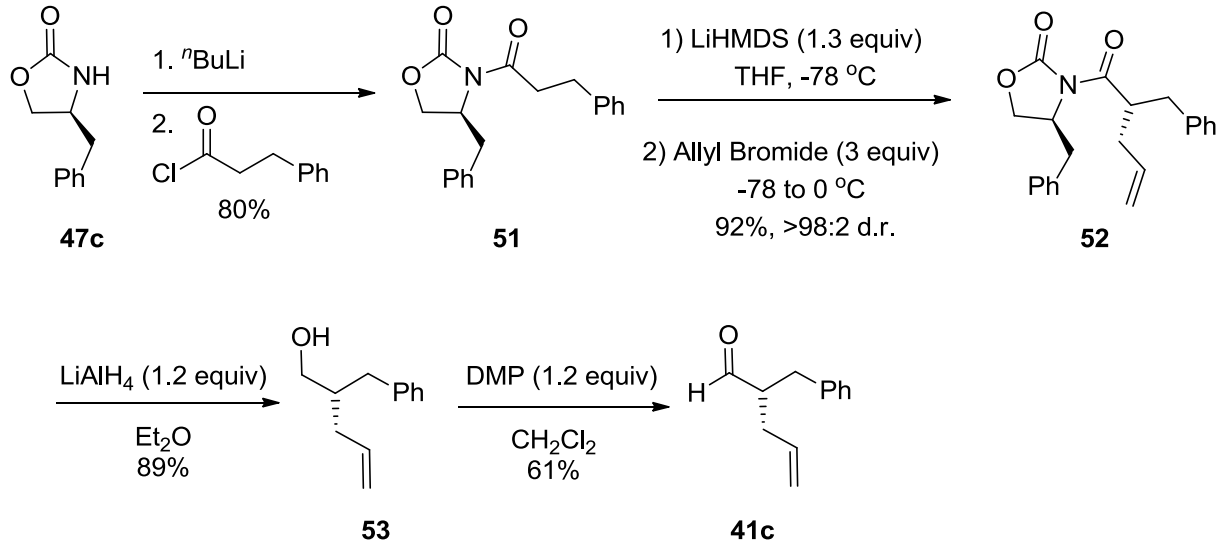
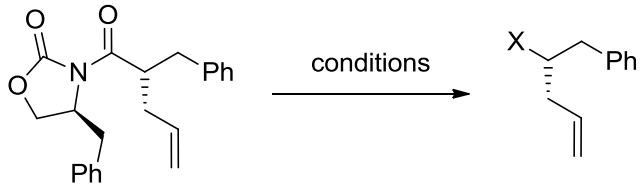
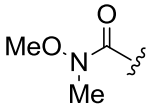


Table 1. Optimization of Conditions for Chiral Auxiliary Cleavage.



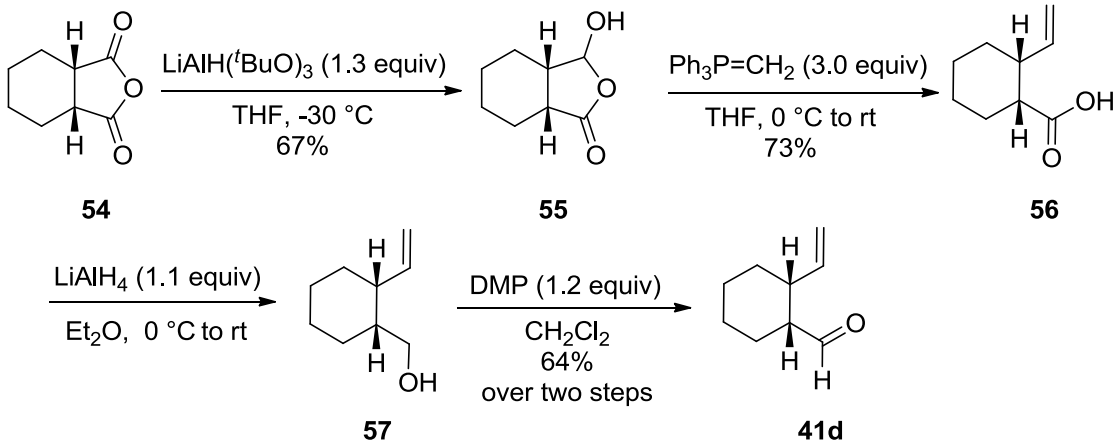
entry	conditions	X	isolated yield (%)
1.	$LiBH_4$ (2.1 equiv) THF/Et_2O	$-CH_2OH$	25
2.	$AlMe_3$ (3.1 equiv) MeNHOMe·HCl (3.1 equiv) THF, 0 °C		complex mixture/ inseparable
3.	DIBAL (1.1 equiv) CH_2Cl_2, -78 °C 1–3 h	-CHO	17
4.	DIBAL (2.0 equiv) CH_2Cl_2, -78 °C 1–3 h	-CHO	20
5.	$LiAlH_4$ (1.2 equiv) Et_2O, 0 °C to rt	$-CH_2OH$	89

Initial attempts to cleave the auxiliary in **52** were met with undesirable crude products, offering little but difficult-to-purify substances leading to low yields. The cleavage conditions examined are outlined in Table 1. Originally the plan was to follow similar conditions as used to access alcohol **50**, however they proved to produce undesirable yields in this case, in a number of trials (entry 1). In a slightly different approach, efforts were put toward cleaving the oxazolidinone and assembling in its place a Weinreb amide (entry 2), with the intention of oxidatively cleaving the resulting moiety to afford the aldehyde directly.[115] Unfortunately, initial attempts were met with only recovered starting material. Subsequent trials yielded an apparent desired Weinreb amide, however this was inseparable from the cleaved oxazolidinone. Following this, a number of attempts at careful reduction of the oxazolidinone with DIBAL to afford the aldehyde directly were undertaken (entries 3 and 4).[116] This was an especially attractive avenue since it would bypass the alcohol altogether. Though the reaction was performed cleanly, with no over reduction to the alcohol, yields were too low to be considered useful, so this route was also abandoned after many attempts, with variable reaction times and careful temperature control.

Finally, reduction with lithium aluminum hydride easily cleaved the auxiliary to the alcohol (entry 5); by this point the hitherto hope of accessing the **41c** directly from **52** was abandoned with little reservation.

Following the completion of **41b** and **41c**, focus shifted from α-alkyl substituted aldehydes to substrates that upon eventual ring-closing would afford a fused-ring system. The first such candidate was *cis* β-vinylcyclohexanecarbaldehyde (**41d**). To begin, anhydride **54** was reduced to the lactol with lithium aluminum tri-*tert*-butoxy hydride,[117] and then subjected to Wittig chemistry to afford the unsaturated carboxylic acid **56**. Initial attempts at accessing the aldehyde consisted of reduction of the carboxylic acid to the alcohol followed by a Swern oxidation. However, the latter failed to give acceptable results, with yields of about 20% resulting repeatedly. Use of Dess-Martin periodinane was settled upon, as yields from these conditions were much more satisfactory. Moreover, this approach permitted the use of alcohol **57** as a crude material, thereby expediting access to the desired aldehyde **41d** (Scheme 31).

Scheme 31. Synthesis of Diastereomerically-Pure *cis*-β-Vinylcyclohexanecarbaldehyde.

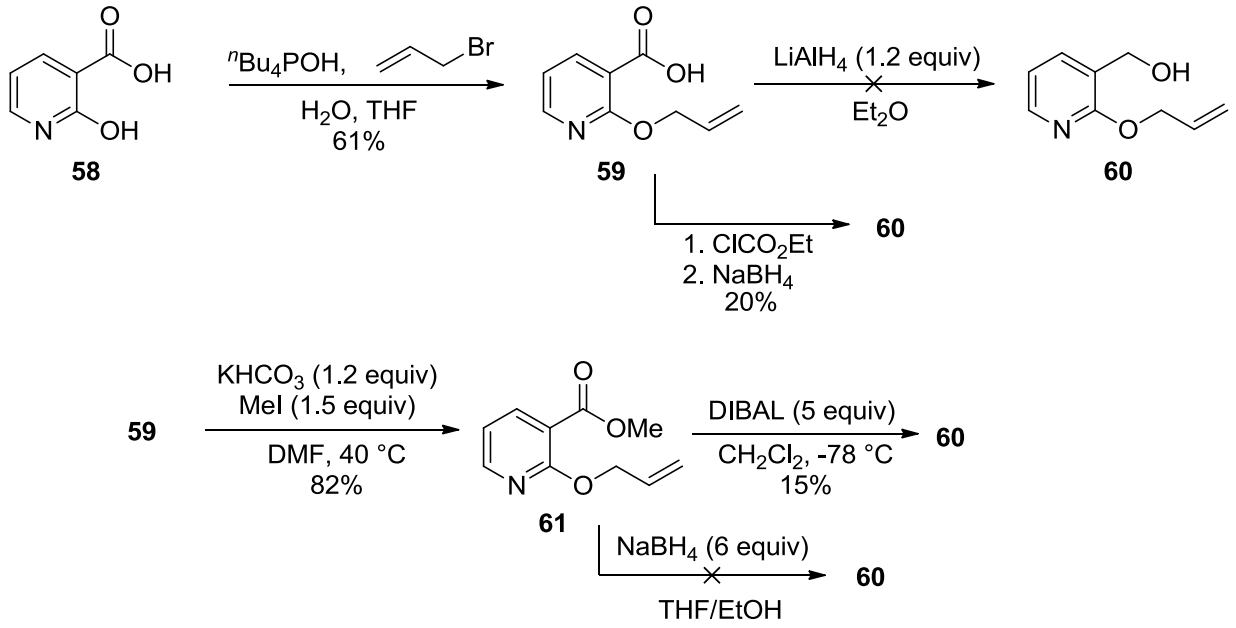


With this work towards aliphatic fused-ring products underway, efforts were next directed toward the complimentary aromatic substrates. This represented the first such foray into the realm of desired product enones with greater than six members in the ring. More specifically, it was rationalized that by beginning with 2-hydroxynicotinic acid (**58**), converting the phenol into an allyloxy unit, followed by formal reduction of the carboxylic acid would give the aldehyde. Upon allylation of the aldehyde and divergent metathesis and oxidation/isomerization would

give seven and eight-membered enones with an interesting heteroatom makeup of the fused bicycle.

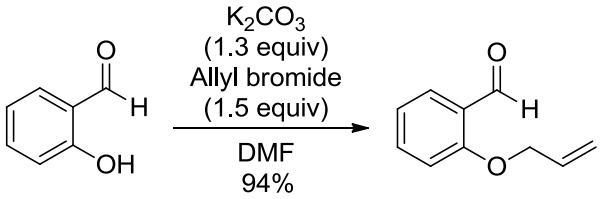
As outlined in Scheme 32, such a plan was put into action, beginning with assembly of allyloxy nicotinic acid **59**. It was at this point that the electronic effects of the nicotinic system made their implications known, as a variety of reduction conditions were met with decomposition and over-reduced substrates. A two-step procedure involving mixed anhydride formation with ethyl chloroformate followed by borohydride reduction was met with low yields, particularly due to isolation issues of the resulting alcohol, which was highly water soluble and difficult to extract with polar organic solvent. Conversion of **59** in to its methyl ester **61** was performed smoothly, in hopes that this species would be amenable to DIBAL reduction, unfortunately similar yields were obtained as seen in the preceding chloroformate/borohydride route from **59**. Finally, a borohydride reduction of **61** was attempted, which resulted in decomposition. These negative results combined with the inherent difficulty in handling the desired alcohol **60** prompted a rethinking of the synthetic strategy, and led to the abandonment of the nicotinic acid system altogether in favour of a more electronically suitable substrate.

Scheme 32. Efforts Toward 2-(Allyloxy)nicotinaldehyde From 2-Hydroxynicotinic Acid: Reduction Attempts Toward the Alcohol.



As the nicotinic acid substrate was repeatedly offering little else than poor yields and starting material decomposition, deletion of the nitrogen in favour of a carbon by switching to commercially available salicylic acid seemed the most logical course of action in order to increase robustness but still maintain the basic framework desired. The short synthetic route to **41e** shown in Scheme 33 was executed considerably more rapidly than the schemes described above, since the requisite aldehyde was already present in the starting material.[118]

Scheme 33. One-Step Synthesis of 2-(Allyloxy)benzaldehyde.

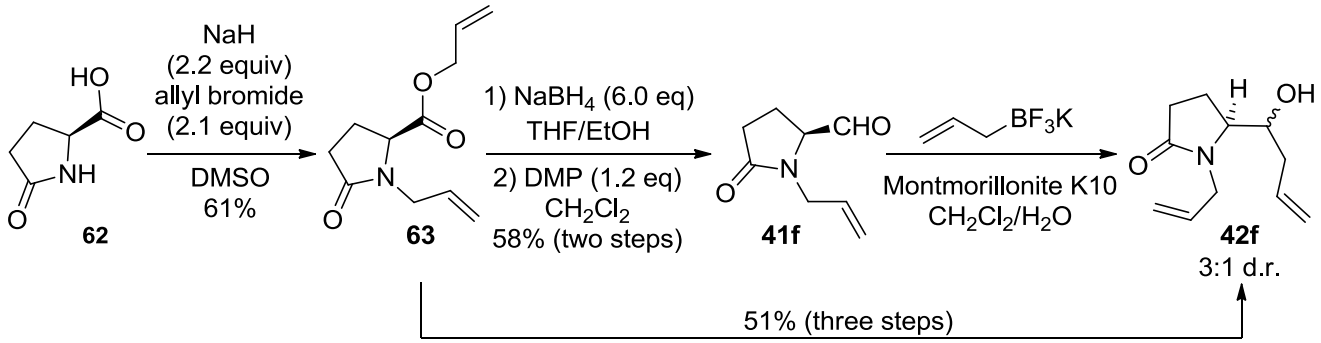


41e

As a final substrate class, it was decided to consider a scaffold more amenable to the possibility of accessing natural product motifs such as alkaloids. The common tendency for alkaloid molecules to bear a number of fused rings was exploited, and with this in mind L-pyroglutamic acid was chosen as a starting material. Beginning with a global alkylation with allyl bromide, the ester was reduced to the alcohol with sodium borohydride. Preliminary isolation attempts of this alcohol were successful, however owing to the polarity of the product, elution times during flash chromatography were quite long, and were marked by visible impurities co-eluting with the alcohol, thereby lowering overall yield. To combat this, it was decided to telescope the process, as the desired aldehyde **41f** (Scheme 34) would be theoretically less polar, and therefore easier to purify by flash chromatography.

This approach worked well, and yields over the ester → alcohol → aldehyde sequence increased compared with that in which purification of each was performed. Subsequently it was postulated whether or not this telescoping approach could be applicable to the following step as well, thereby eliminating the purification of **41f**. The innate selectivity of the allylation chemistry was reason enough to assume the crude **41f** would not present any significant problems in this regard. Once again, this proved to be a productive approach, affording a 51 % isolated yield of **42f** over three steps.

Scheme 34. Telescoping Approaches to Synthesis of (*S*)-1-Allyl-5-oxopyrrolidine-2-carbaldehyde and (*S*)-1-Allyl-5-((*R*)-1-hydroxybut-3-en-1-yl)pyrrolidin-2-one From L-Pyroglutamic Acid.

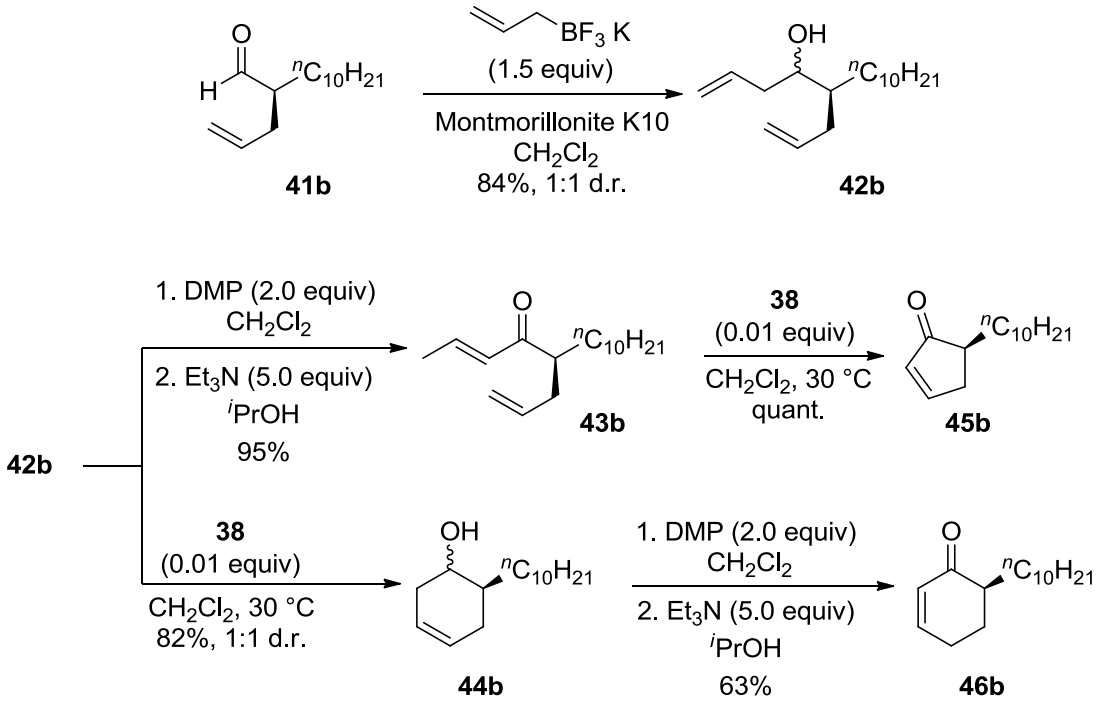


With these aldehydes **41** in hand, attention turned from assembling the substrates to employing the key aldehyde allylation chemistry that this work was meant to showcase.

5.3 Allylation of Aldehydes and Divergent Syntheses of α,β-Unsaturated Ketones

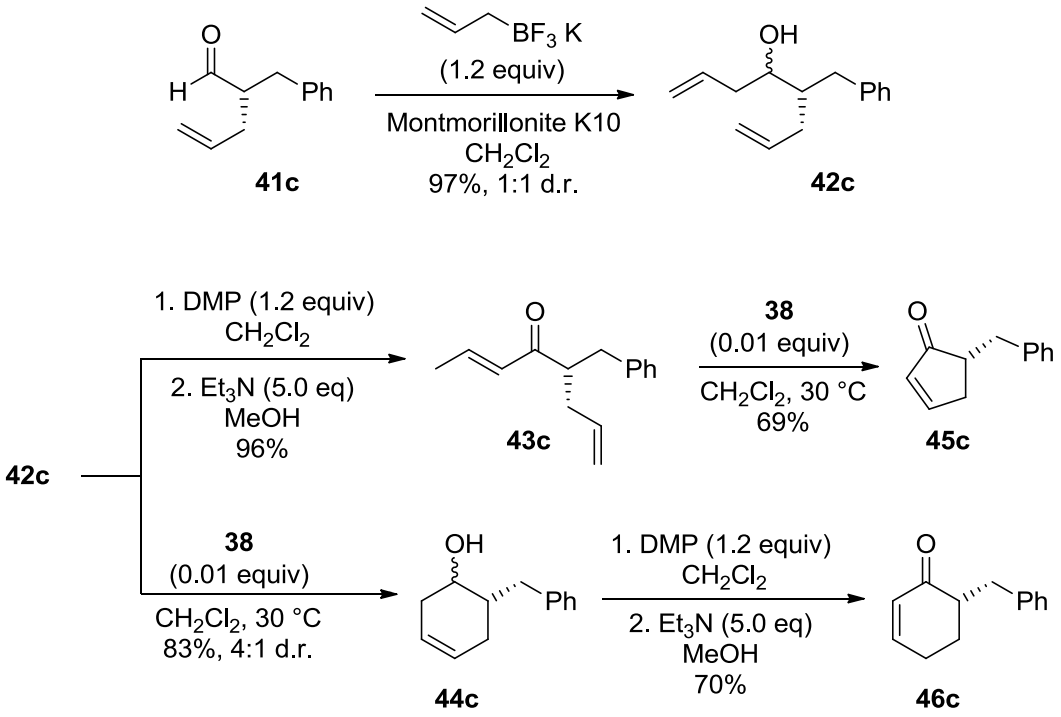
In contrast to some of the difficulties encountered in Section 5.2, the chemistry outlined in this section was more successful, and steps were carried out relatively quickly and easily. Beginning with the aldehyde **41b**, the montmorillonite-catalyzed allylation with potassium allyltrifluoroborate was carried out and the resulting homoallylic alcohol **42b** was obtained in good yield (Scheme 35) after a simple filtration to purify. From this point the divergent synthesis of both five- and six-membered enones were carried out quickly and easily, using 1% Grubbs' second-generation catalyst **38** to effect smooth ring closure. Remarkable was the quantitative acquisition of cyclopentenone **45b** after RCM.[119] DMP was chosen as the oxidant of choice based on its ease of use and the mild conditions required, as well as the capacity for simply adding more oxidant to a reaction to drive it to completion. As such, DMP oxidation is much more facile than Swern conditions, for example. PCC on silica may be used as an alternative, but purification of such oxidation reactions is less straight-forward than with DMP.

Scheme 35. Allylation of (*S*)-2-Allyldodecanal and Divergent RCM & Oxidation/Isomerization Toward α-*n*-Decyl Enones.



In a similar fashion, the allylation chemistry was applied to aldehyde **41c** to afford the common intermediate homoallylic alcohol **42c** (Scheme 36). Although the ring RCM to give cyclopentenone **45c** was less than 70%, which is in stark contrast to the quantitative yield obtained for related pentenone **45b** (Scheme 35), the yields obtained for enone **46d**[120] as well as the other species shown in Scheme 35, were good to excellent, and represent an improvement over those of the preceding scheme, better exemplifying the synthetic utility of this chemistry.

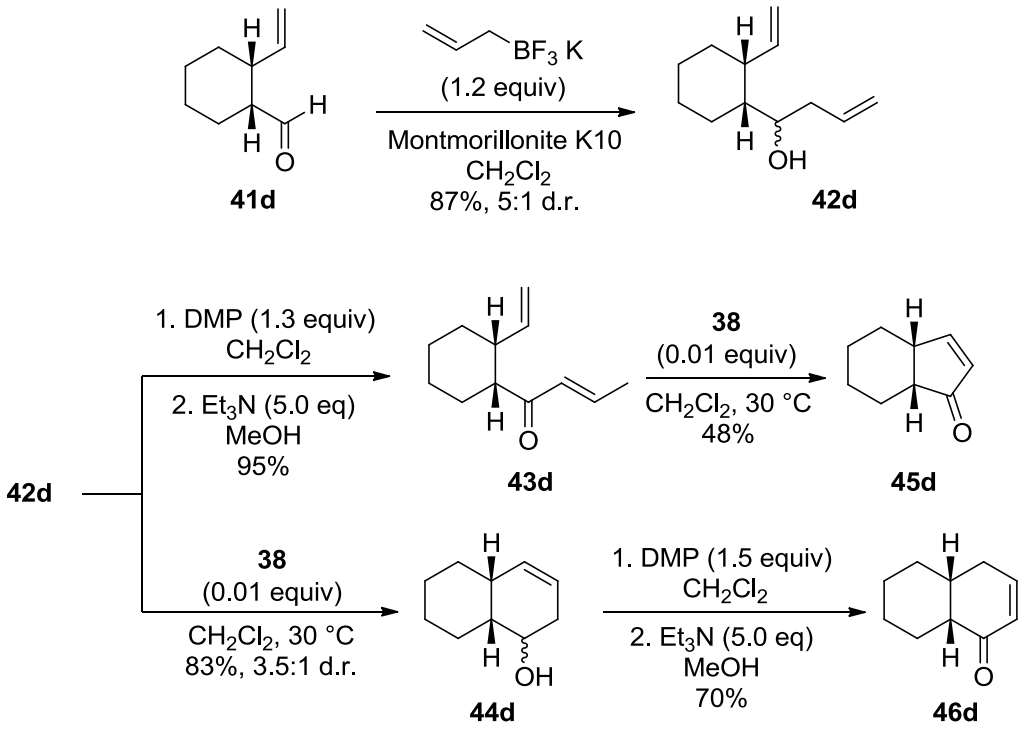
Scheme 36. Allylation of (*S*)-2-benzylpent-4-enal and Divergent RCM & Oxidation/Isomerization Toward α-Benzyl Enones.



Having completed the entirety of the desired synthetic sequences on the analogous substrates **41b** and **41c**, it was with particular zeal that attention was directed toward aldehyde **41d**,[121] which was allylated in the usual fashion and with the usual high yielding result (Scheme 37). Carrying out the initial steps of each divergent pathway was incident-free; however the following steps to furnish the enones were considered with trepidation, due to the possible volatility and/or *cis*- to *trans*-isomerization of the fused ring products. Nevertheless, the usual RCM and oxidation/isomerization procedures were executed, and the low-yielding result of pentenone **45d** seemed to verify concerns about volatility. Fortunately though, there was no apparent

isomerization to the *trans* isomer in either of the enones even after treatment with base. And because the potential volatility of enone **46d** was also a concern, the good yield obtained was gratifying.

Scheme 37. Allylation of (1*R*,2*R*)-2-Vinylcyclohexanecarbaldehyde and Divergent RCM & Oxidation/Isomerization Toward *cis*-5,6-Fused Cyclohexyl Enones.



And so was concluded the divergence toward five- and six-membered enones. Focus then shifted to larger rings, beginning with the salicaldehyde-derived **41e**. After allylation, the homoallylic alcohol intermediate was taken and transformed into the seven-membered enone **45e**, constituting the first foray with this methodology toward ring sizes greater than six. Such success was short-lived however, as efforts toward the eight-membered enone with the usual RCM conditions were futile. A number of conditions were tried, with catalyst loading and temperature being varied on alcohol **42e** (Table 2, entries 1−6).[122] Precedence for similar benzene systems with *ortho*-fused olefins to undergo RCM to afford eight-membered rings are known, with particular credit given to the conformational rigidity imposed by the aromatic ring, forcing the olefins into proper orientation for metathesis.[123]

Scheme 38. Allylation of 2-(Allyloxy)benzaldehyde and Divergent RCM & Oxidation/Isomerization Attempts Toward Seven- and Eight-Membered Enones.

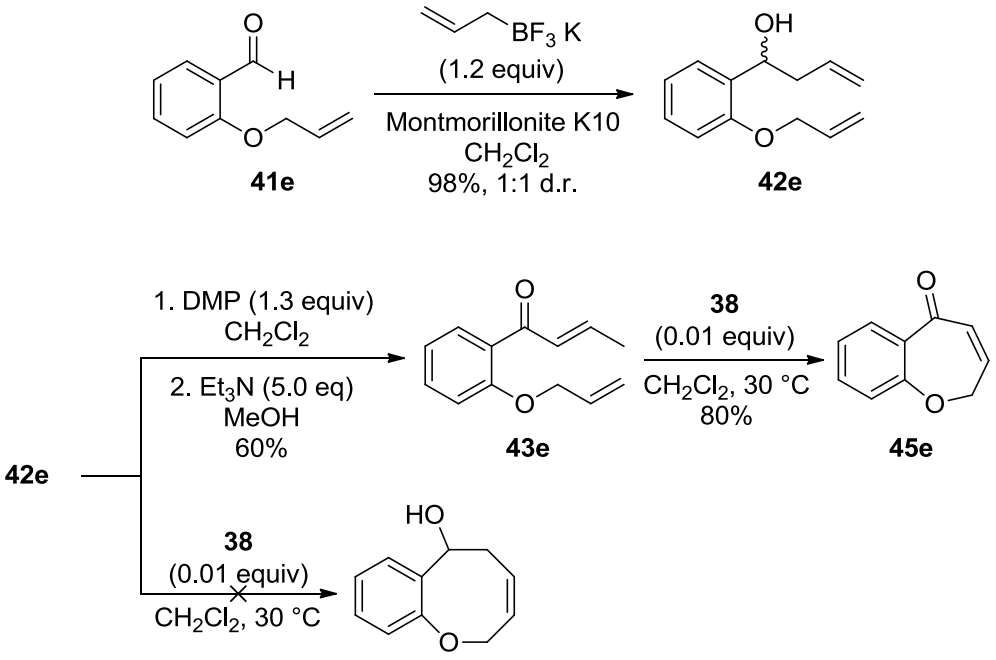
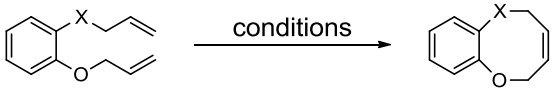


Table 2. RCM Efforts toward an Eight-Membered Ring.



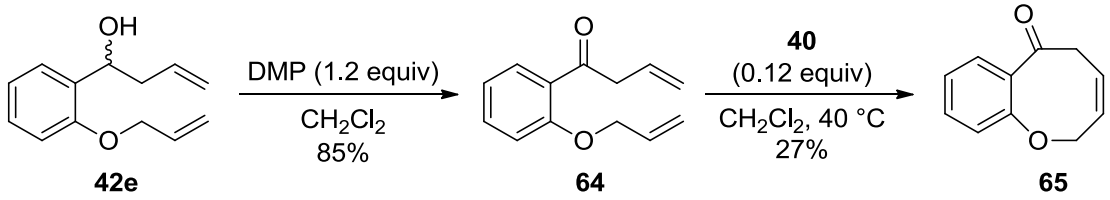
entry	X	°C	catalyst	equiv	solvent	time (h)	yield (%)
1		30	**38**	0.01	CH_2Cl_2	16	-
2		reflux	**38**	0.02	CH_2Cl_2	20	-
3		55	**38**	0.08	PhMe	6	-
4		55	**38**	0.08	PhMe	22	-
5		55	**38**	0.12	PhMe	120	-
6		reflux	**38**	0.21[a]	CH_2Cl_2	20	-
7		55–95	**38**	0.08	PhMe	360	-
8		40	**40**	0.09[b]	CH_2Cl_2	10	27

[a] 0.07 equiv at first, then another 0.07 equiv after three hours, and six hours.
[b] 0.06 equiv at first, then another 0.03 equiv after four hours, and eight hours.

Though the requisite *ortho*-substituted aromatic ring was also present in **42e**, it was felt that further rigidity could be imposed, namely by oxidizing alcohol **42e** to the corresponding allyl

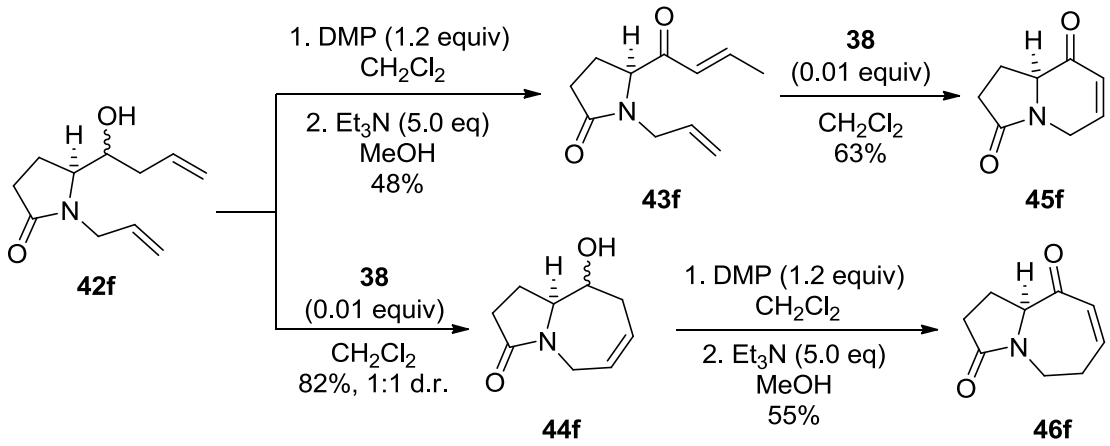
ketone **64**. This proved to be an ineffective endeavour when RCM was attempted with catalyst **38** (entry 7), however switching to the Hoveyda–Grubbs second-generation catalyst **40** the desired eight-membered ring **65** was afforded in 27% yield (Scheme 39), with no isomerization to the α,β-unsaturated enone noted. It is postulated that the increased thermal stability of this catalyst allowed it to properly catalyze the reaction in refluxing dichloromethane.[100] Though this transformation required a relatively high catalyst loading in relation to the overall yield, this is comparable to results described recently by Sorensen and co-workers in the synthesis of pleuromutilin.[124] Subjecting this β,γ-unsaturated ketone to triethylamine in anhydrous methanol in an effort to isomerize to the α,β-unsaturated enone was ineffective. DBU was tried as well, with hopes that its greater basicity would better drive the isomerization, however after the usual three hours at room temperature the reaction yielded a thick brown tar, uncharacterizable even after flash chromatography. Further trials, including increased equivalency of triethylamine (10 equiv), as well as heating to 40 °C, were ineffective and afforded only starting material. Efforts to access the eight-membered enone are ongoing.

Scheme 39. Access to Eight-Membered Ring Using Hoveyda–Grubbs Second-generation Catalyst.



Utilizing the homoallylic alcohol **42f** obtained through the telescoping ester reduction/oxidation/allylation sequence shown in Scheme 34, the divergent synthesis of 5,6- and 5,7-fused azabicyclic enones was achieved through the usual method (Scheme 40). **43f** and **45f** were obtained successfully, though the slightly low yield of the former is noted. The ease with which the seven-membered ring of **44f** was obtained is notable, as large ring sizes are notoriously difficult to form. Oxidation and isomerization to **46f** was straightforward, though purification required multiple chromatographic procedures, which is a likely reason for the low yield.

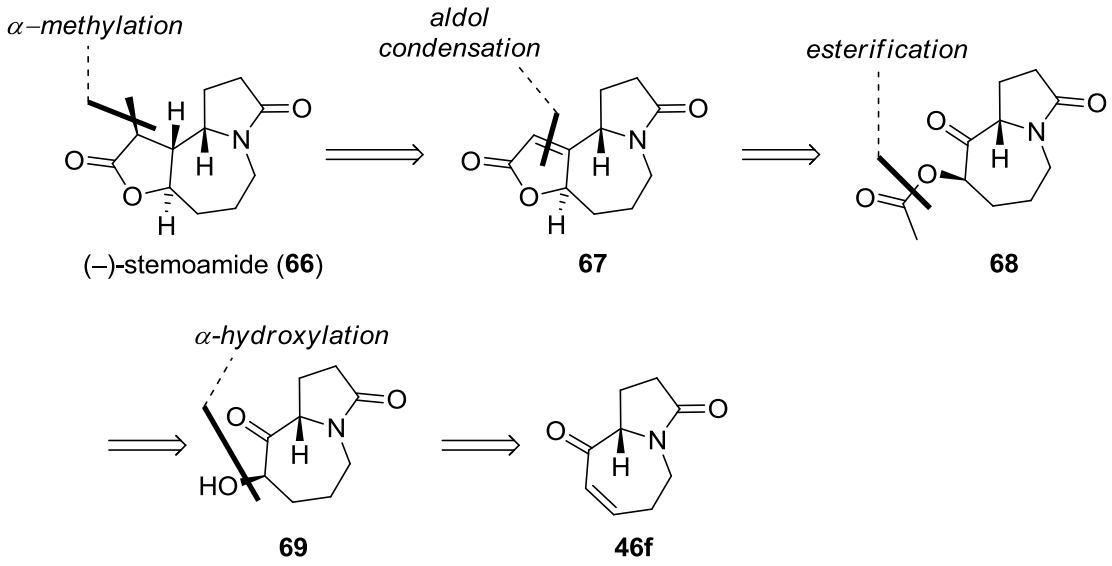
Scheme 40. Divergent RCM & Oxidation/Isomerization Toward 5,6- and 5,7-Fused Azabicyclic Enones.



5.4 Potential Natural Product Synthesis

Enone **46f** bears the 5,7-fused *aza*bicyclic core present in alkaloids of the stemona family, a natural product class that has received considerable attention recently, owing to their interesting biological properties, as well as their interesting structures.[109] Although time restraints prevented the investigation in to such a total or formal synthesis, the proposed retrosynthetic pathway from (–)-stemoamide (**66**) is outlined in Scheme 41. The lead-off α-methylation disconnection has been previously reported by Somfai and co-workers, thus constituting the synthesis of lactone **67** as a formal synthesis of the target **66**. Further disconnections reveal potential for an aldol condensation to **67** from ester **68**, which itself derives from the acylation of **69** with acetyl chloride, for example. An α-hydroxylation (e.g., Rubottom oxidation)[125] of a reduced form of **46f** would complete the pathway.

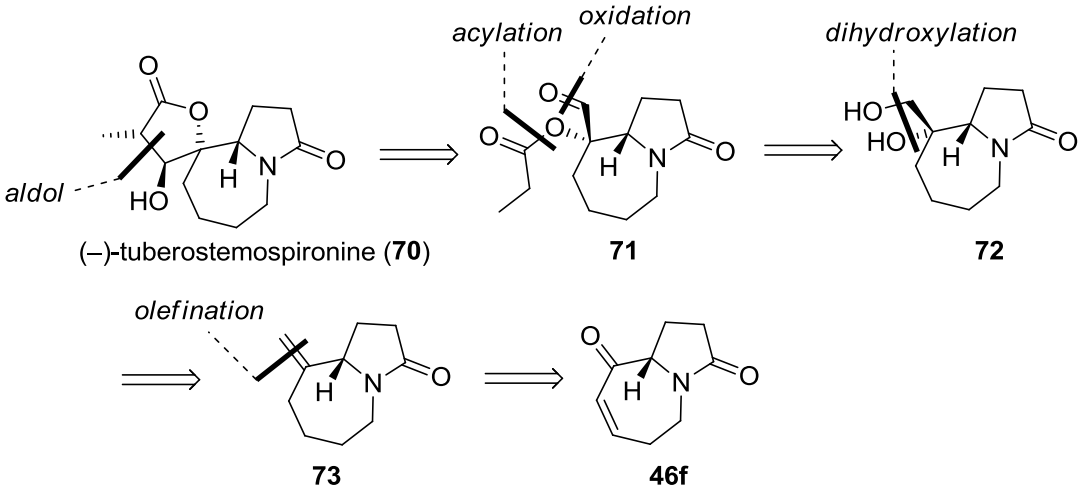
Scheme 41. Proposed Retrosynthetic Pathway to (–)-Stemoamide from Enone **46f**.



In a conceptually similar, though potentially longer, synthetic route to the related stemona alkaloid (–)-tuberostemospironine **70** (Scheme 42), it is proposed that the same enone **46f** could be utilized as a starting point owing to the requisite carbon skeleton. Disconnecting from the target, an intramolecular aldol reaction is possible between the ethyl ester and aldehyde, both accessible from the dihydroxylated intermediate **72**. This is ostensibly derived from a stereoselective dihydroxylation of olefin **73**, which would be accessible from enone **46f** through

a reduction of the olefin and Wittig-type olefination. A total synthesis of target molecule **70** is currently unreported in the literature.

Scheme 42. Proposed Retrosynthetic Pathway to (–)-Tuberostemospironine from Enone **46f**.



6 Conclusions and Recommendations

The work described herein describes the utility and facility of the montmorillonite-catalyzed allylation chemistry previously developed in the Batey group.[80f] It has been shown that this methodology has application toward the synthesis of synthetically useful homoallylic alcohols, which may be used in a divergent manner to afford cyclic α,β-unsaturated ketones through ring-closing metathesis and oxidation/isomerization sequences. The limitation of this chemistry falls primarily on acquisition of the necessary aldehyde precursors, and the ring size of the desired products.

Having achieved synthesis of the desired enones, one may utilize them toward the synthesis of related natural products, as was seen in the relationship between **46f** and various stemona alkaloids.[109] A similar relationship to enone **45f** can be seen in the alkaloids featured in Scheme 4. Finally, unpublished results regarding addition of potassium crotyltrifluoroborate to aldehydes to afford α-methyl enones may be further elaborated in this divergent fashion should it be deemed to be of synthetic interest.

Chapter 3
Experimental

General Synthetic Methods

Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. CH_2Cl_2 was distilled from CaH_2 under nitrogen. All reagents, unless otherwise stated, were used as received (Aldrich, Fisher Scientific Ltd. or Lancaster). Commercially available potassium allyl trifluoroborate and Dess-Martin periodinane[126] were prepared by known literature procedures. Montmorillonite K10 was purchased from Aldrich, and was used without activation.

IR spectra were obtained on a Perkin-Elmer Spectrum 1000, with samples loaded as films on NaCl plates. ^1H and ^{13}C NMR spectra were obtained on Varian Mercury 300 or Unity 400 and Bruker 400 spectrometers as solutions in $CDCl_3$ (unless otherwise indicated). Chemical shifts are expressed in ppm values. Spectra were referenced to 7.26 ppm for $CDCl_3$ for proton chemical shifts and 77.00 ppm for $CDCl_3$ for carbon chemical shifts. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (this abbreviation is also used for designation of IR peaks); *J*, coupling constant in Hz. Low resolution mass spectra (MS) were recorded on a Bell and Howell 21-490 spectrometer. High resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.), visualized with a UV lamp (254 nm), 2,4-dinitrophenylhydrazine, Hanessian's stain, iodine, ninhydrin, *p*-anisaldehyde, potassium permanganate, phosphomolybdic acid (Aldrich), or vanillin. References following the compound names indicate literature articles where ^1H and ^{13}C NMR data have previously been reported.

General Procedure (A) for Addition of Potassium Allyltrifluoroborate to Aldehydes. To aldehyde (4.50 mmol), potassium allyltrifluoroborate (5.40 mmol), and montmorillonite K10 (0.900 g) in a 25 mL round bottom flask was added CH_2Cl_2 (12.6 mL) and water (0.90 mL). The biphasic reaction mixture was vigorously stirred at rt for 20 min at which point reaction conversion was determined to be complete as monitored by TLC analysis. The reaction mixture was then filtered to separate the solid phase, washed with CH_2Cl_2 (3 x 15 mL) and the solvent was evaporated under reduced pressure to give the crude material. Purification by flash chromatography on silica gel (Hex/EtOAc) gave the product alcohol.

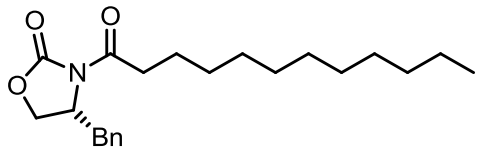
General Procedure (B) for Ring-Closing Metathesis.

To a solution of Grubbs second-generation catalyst (8.5 mg, 0.010 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of alcohol (1.0 mmol) in CH_2Cl_2 (10 mL) in one portion. The reaction mixture was warmed at 30 °C over 1 h under argon. After completion of the reaction the solvent was removed under reduced pressure and crude olefin was dissolved with diethyl ether (65 mL). The resulting solution was washed with water (4 x 5 mL) and activated carbon (1.3 wt equiv of the crude product) was added to the diethyl ether solution and stirred overnight. After the carbon was filtered, the filtrate was concentrated *in vacuo* to provide the desired product. Purification by flash chromatography on silica gel (Hex/EtOAc) afforded the desired carbocycle as a colourless oil.

General Procedure (C) for Oxidation and Isomerisation.

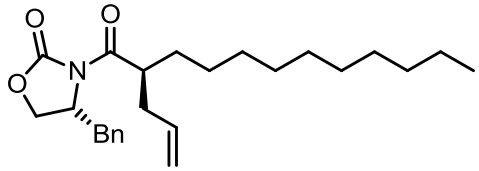
To a round bottom flask containing the alcohol starting material (0.50 mmol) dissolved in CH_2Cl_2 (2.2 mL) was added Dess-Martin periodinane (0.254 g, 0.60 mmol) and stirred at rt under argon. After 2 h the resulting white suspension was diluted with diethyl ether (5 mL) and saturated aqueous sodium bicarbonate (5 mL), then $Na_2S_2O_3$ (0.20 g, 1.26 mmol) was added and the resulting mixture stirred 30 min. Crude ketone was extracted into ethyl acetate or dichloromethane (3 x 5 mL), concentrated *in vacuo*, then dissolved with anhydrous ^{i}PrOH or MeOH (2 mL). Triethylamine (0.350 mL, 2.5 mmol) was added and stirred for 3 h. ^{i}PrOH was evaporated *in vacuo*, the residue was diluted with diethyl ether (4 mL) and washed with saturated aqueous NH_4Cl (2 x 2 mL), water (2 mL) and dried ($MgSO_4$). Solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (Hex/EtOAc) to give the desired enone.

(*R*)-4-Benzyl-3-dodecanoyloxazolidin-2-one (48)[111]



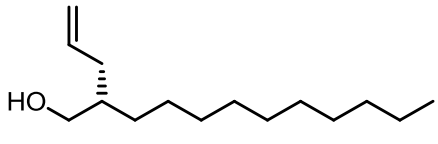
Modified from the literature procedure. R_f = 0.30 (1:9 EtOAc/Hexanes), clear oil, 0.841 g (75% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.38 (5H, m), 4.67 (1H, s), 4.12–4.23 (2H, m), 3.30 (1H, dd, *J* = 13.0, 3.5 Hz), 2.83–3.04 (2H, m), 2.76 (1H, dd, *J* = 13.0, 9.5 Hz), 1.60–1.74 (2H, m), 1.18–1.43 (14H, m), 0.82–0.93 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 35.7, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 24.5, 22.9, 14.3, (one carbon missing).

(*R*)-3-((*S*)-2-Allyldodecanoyl)-4-benzyloxazolidin-2-one (49)



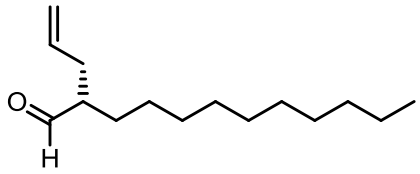
To a solution of diisopropylamine (0.38 mL, 2.7 mmol) in THF (3 mL) at -78 °C was added ^{n}butyllithium (2.45 M, 1.07 mL, 2.6 mmol). After stirring for 40 min under argon this was cannula-transferred in to a solution of **48** (0.804g, 2.2 mmol) in THF (12 mL) and stirred 45 min at -78 °C. Allyl bromide (0.95 mL, 11.0 mmol) was then added dropwise. After stirring for 30 min the reaction was warmed to 0 °C and stirred for 30 min, and then quenched with sat. $KHSO_4$. Extraction in ethyl acetate and flash chromatography (1:9 EtOAc/Hexanes) gave the product as a clear oil, R_f = 0.40, 0.704 g (79% yield); $[\alpha]_D^{26}$ = -43.1 (*c* = 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.39 (5H, m), 5.83 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz), 4.97–5.16 (2H, m), 4.69 (1H, dddd, *J* = 10.0, 7.0, 3.5, 3.5 Hz), 4.08–4.23 (2H, m), 3.91 (1H, dddd, *J* = 8.0, 8.0, 6.0, 6.0 Hz), 3.30 (1H, dd, *J* = 13.0, 3.0 Hz), 2.66 (1H, dd, *J* = 13.5, 10.0 Hz), 2.39–2.54 (1H, m), 2.25–2.39 (1H, m), 1.63–1.81 (1H, m), 1.49 (1H, dd, *J* = 14.5, 6.0 Hz), 1.15–1.35 (16H, m), 0.80–0.93 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 153.3, 135.7, 135.5, 129.6, 129.1, 127.5, 117.2, 66.1, 55.7, 42.5, 38.3, 37.0, 32.1, 31.8, 29.9, 29.8, 29.6, 29.5, 27.4, 22.9, 14.3, (one carbon missing); IR (film) ν 2924, 2854, 1782, 1700, 1386, 1208; MS (ESI) *m/z* 400 (100), 171 (7); HRMS (ESI) *m/z* ($C_{25}H_{38}NO_3^+$) calcd. 400.2852, found 400.2858.

(*S*)-2-Allyldodecan-1-ol (50)



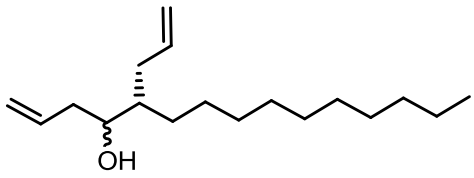
To a solution of **49** (0.685 g, 1.71 mmol) in diethyl ether (40 mL) was added a solution of $LiBH_4$ (0.070 g, 3.2 mmol) in THF (10 mL). The reaction was stirred under argon at room temperature overnight and then poured into 100 mL of a saturated solution of Rochelle's salt. Extraction in ethyl acetate and flash chromatography (1:9 EtOAc/Hexanes) gave the product as a clear oil, R_f = 0.10, 0.181 g (57% yield); $[\alpha]_D^{26}$ = +0.45 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz), 4.96–5.12 (2H, m), 3.50–3.60 (2H, m), 2.08–2.17 (2H, m), 1.52–1.66 (1H, m), 1.20–1.35 (16H, m), 0.81–0.95 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 116.3, 65.8, 40.6, 36.0, 32.1, 30.8, 30.1, 29.8, 29.8, 29.5, 27.1, 22.9, 14.3, (one carbon missing); IR (film) ν 3356, 2923, 2853, 1465, 1042, 901; MS (ESI) *m/z* 227 (100), 209 (7), 163 (10), 149 (5); HRMS (EI) *m/z* ($C_{15}H_{31}O^+$) calcd. 227.2375, found 227.2370.

(*S*)-2-Allyldodecanal (41b)



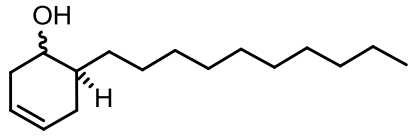
To a solution of **40** (0.169 g, 0.750 mmol) in CH_2Cl_2 (4 mL) was added DMP (0.637 g, 1.50 mmol) and after stirring under argon at room temperature for 2.5 h the alcohol starting material was consumed as monitored by TLC. The reaction was quenched with 0.5 g $Na_2S_2O_3$ in 1.5 mL each diethyl ether and saturated sodium bicarbonate solution. Extraction in diethyl ether and flash chromatography (1:9 EtOAc/Hexanes) gave the product as a clear oil, R_f = 0.65, 0.0935 g (56% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, d, *J* = 2.5 Hz), 5.67–5.81 (1H, m), 5.01–5.14 (2H, m), 2.30–2.46 (2H, m), 2.19–2.29 (1H, m), 1.59–1.70 (1H, m), 1.41–1.53 (1H, m), 1.19–1.38 (16H, m), 0.83–0.92 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 135.2, 117.3, 51.5, 33.2, 29.8, 32.1, 29.7, 29.7, 29.6, 29.5, 28.6, 27.1, 22.9, 14.3; IR (film) ν 2924, 2854, 1732, 1458, 914.

(5*S*)-5-allylpentadec-1-en-4-ol (42b)



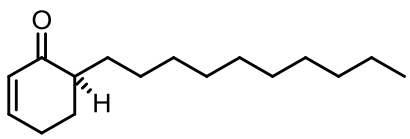
Prepared from **41b** according to the general procedure (A). Clear Oil, 0.091 g (84% crude yield); ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mixture of diastereomers) δ 5.72–5.91 (2H, m), 4.93–5.19 (4H, m), 3.60–3.71 (1H, m), 2.01–2.36 (4H, m), 1.46–1.64 (2H, m), 1.35–1.46 (2H, m), 1.17–1.35 (16H, m), 0.84–0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.8, 135.8, 135.7, 118.1, 118.0, 116.2, 116.1, 72.4, 43.0, 39.1, 38.9, 35.0, 34.0, 32.1, 30.2, 29.9, 29.8, 29.8, 29.8, 29.5, 28.8, 27.6, 27.4, 22.9, 14.3; IR (film) ν 3418, 3077, 2953, 2923, 2854, 1247, 910; MS (EI) *m/z* 248 (3), 225 (100), 207 (15), 169 (34), 109 (21), 95 (30), 81 (20); HRMS (EI) *m/z* ($C_{18}H_{32}O^{+}$) calcd. 248.2504, found 248.2508.

(6*S*)-6-Decylcyclohex-3-enol (44b)



Prepared from **42b** according to the general procedure (B). Clear oil, R_f = 0.17 (1:9 EtOAc/Hexanes), 0.0187 g (68% yield); ^{1}H NMR (300 MHz, $CDCl_3$) (1:1 mixture of diastereomers) δ 5.48–5.78 (2H, m), 3.96 (1H, br s), 3.56–3.69 (1H, m), 1.53–2.45 (7H, m), 1.07–1.37 (16H, m), 0.80–0.93 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.2, 127.0, 126.5, 124.0, 123.4, 68.2, 51.9, 40.1, 32.1, 31.9, 31.9, 30.2, 30.0, 29.8, 29.8, 29.5, 27.3, 27.3, 26.8, 22.9, 14.34; IR (film) ν 3386, 3022, 2953, 2923, 2853, 1739, 1465, 1047; MS (EI) *m/z* 220 (100), 79.1 (22); HRMS (EI) *m/z* ($C_{16}H_{30}O^{+}$) calcd. 238.2297, found 238.2300.

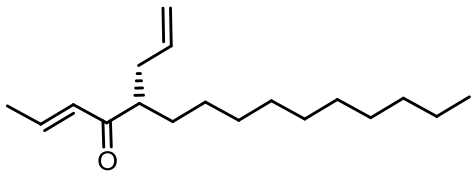
(*S*)-6-Decylcyclohex-2-enone (46b)



Prepared from **44b** according to the general procedure (C). Clear oil, R_f = 0.23 (1:9 EtOAc/Hexanes), 0.0107 g (63% yield); $[a]_D^{24}$ = -9.2 (*c* = 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62–5.86 (2H, m), 2.76–3.02 (2H, m), 2.44–2.68 (2H, m), 2.06–2.22 (1H, m), 1.71–1.89 (1H, m), 1.20–1.35 (17H, m), 0.84–0.92 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ

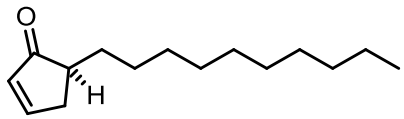
211.8, 126.6, 124.5, 104.9, 48.2, 40.5, 32.7, 32.1, 29.9, 29.8, 29.7, 29.5, 29.4, 27.3, 22.9, 14.3; IR (film) ν 3031, 2923, 2853, 1679, 1458, 1386, 1219, 1117; MS (ESI) *m/z* 279 (4), 254 (30), 237 (100), 219 (6), 171 (5); HRMS (EI) *m/z* ($C_{16}H_{29}O^+$) calcd. 237.2218, found 237.2214.

(*S,E*)-5-Allylpentadec-2-en-4-one (43b)



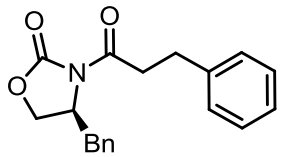
Prepared from **42b** according to the general procedure (C). Clear oil, 0.0311 g (95% crude yield); $[\alpha]_D^{26}$ = +7.5 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, dq, *J* = 15.53, 6.84 Hz), 6.10–6.26 (1H, m), 5.70 (1H, dddd, *J* = 17.0, 10.0, 7.00, 7.00 Hz), 4.89–5.08 (2H, m), 2.74 (1H, tt, *J* = 8.0, 6.0 Hz), 2.29–2.44 (1H, m), 2.07–2.23 (1H, m), 1.90 (2H, dd, *J* = 7.0, 1.5 Hz), 1.53–1.71 (1H, m), 1.35–1.51 (1H, m), 1.14–1.35 (m, 16 H), 0.80–0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.32, 142.78, 136.20, 131.52, 116.58, 49.42, 36.19, 32.12, 31.73, 29.96, 29.81, 29.67, 29.53, 27.51, 22.90, 18.52, 14.33; IR (film) ν 2953, 2924, 2854, 1740, 1698, 1628, 1443, 1378; MS (EI) *m/z* 207 (7), 163 (72), 149 (54), 105 (100); HRMS (EI) *m/z* ($C_{18}H_{32}O^+$) calcd. 264.2453, found 264.2457.

***(S)*-5-Decylcyclopent-2-enone (45b)**[119]



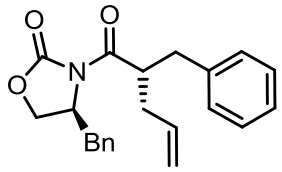
Prepared from **43b** according to the general procedure (B). Clear oil, quantitative yield; $[\alpha]_D^{25}$ = +11.4 (*c* = 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.69 (1H, m), 6.16–6.19 (1H, m), 2.89 (1H, ddd, *J* = 6.5, 3.0, 2.0 Hz), 2.82–2.86 (1H, m), 2.39 (1H, q, *J* = 2.5 Hz), 2.33–2.35 (1H, m), 2.31 (1H, dddd, *J* = 6.5, 4.58, 2.0, 2.0 Hz), 1.81 (1H, ddd, *J* = 9.0, 6.5, 4.0 Hz), 1.26 (8H, s), 0.85–0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 163.6, 134.1, 45.1, 35.9, 32.1, 31.5, 29.8, 29.7, 29.5, 27.4, 22.9, 14.3; MS (EI) *m/z* 222 (9), 149 (1), 95 (33), 82 (100); HRMS (EI) *m/z* ($C_{15}H_{26}O^+$) calcd. 222.1984, found 222.19867.

(*S*)-4-Benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one (51)[112]



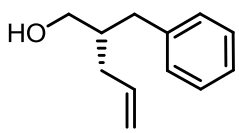
Prepared according to the literature procedure. 1.605 g (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.38 (10H, m), 4.66 (1H, td, *J* = 6.5, 3.5 Hz), 4.06–4.24 (2H, m), 3.16–3.39 (3H, m), 2.91–3.13 (2H, m), 2.75 (2H, dd, *J* = 13.5, 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 153.4, 140.4, 135.1, 129.4, 128.9, 128.5, 128.4, 127.3, 126.2, 66.1, 55.1, 37.8, 37.1, 30.2.

(*S*)-4-benzyl-3-((*S*)-2-benzylpent-4-enoyl)oxazolidin-2-one (52)[112]



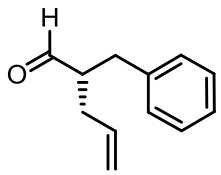
Prepared from **51** according to the literature procedure. 0.704 g (67% yield), ≥98:2 d.r.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.39 (10H, m), 5.86 (1H, dddd, *J* = 17. 0, 10.0, 7.0, 7.0 Hz), 5.02–5.21 (2H, m), 4.45 (1H, dddd, *J* = 10.0, 7.5, 3.5, 2.5 Hz), 4.33 (1H, tt, *J* = 8.5, 6.0 Hz), 4.01 (1H, dd, *J* = 9.0, 2.5 Hz), 3.82 (1H, ddd, *J* = 9.0, 8.0, 0.5 Hz), 3.23 (1H, dd, *J* = 13.5, 3.5 Hz), 2.81–2.99 (2H, m), 2.64 (1H, dd, *J* = 13.5, 10.0 Hz), 2.51–2.60 (1H, m), 2.31–2.40 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 139.1, 135.6, 135.2, 129.6, 129.3, 129.1, 128.5, 127.5, 126.6, 117.6, 66.0, 55.7, 44.1, 38.5, 38.2, 36.5.

(*S*)-2-Benzylpent-4-en-1-ol (53)[114]



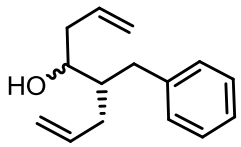
To a solution of **52** (0.458 g, 1.32 mmol) in diethyl ether (10 mL) was added lithium aluminum hydride (0.061 g, 1.60 mmol) at 0 °C and allowed to warm to room temperature overnight, under argon. The reaction was quenched with saturated Rochelle's salt, filtered, and then dried with $MgSO_4$. Flash chromatography (1:4 EtOAc/Hexanes) gave the product as a clear oil, R_f = 0.45, 0.207 g (89% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.38 (5H, m), 5.69–5.95 (1H, m), 4.96–5.18 (2H, m), 3.55 (2H, dd, *J* = 5.0, 2.5 Hz), 2.42–2.74 (2H, m), 2.01–2.22 (2H, m), 1.79–2.01 (1H, m), 1.47–1.66 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 137.0, 129.4, 128.5, 126.1, 116.8, 64.9, 42.6, 37.4, 35.7.

(*S*)-2-Benzylpent-4-enal (41c)[116]



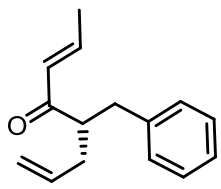
To a solution of **53** (0.208 g, 1.18 mmol) in CH_2Cl_2 (12 mL) was added DMP (0.605 g, 1.43 mmol). The reaction was stirred under argon at room temperature until all starting material was consumed as monitored by TLC analysis, at which point 0.3 g $Na_2S_2O_3$ in 5 mL each CH_2Cl_2 and saturated sodium bicarbonate solution was added to quench. Extraction in CH_2Cl_2 followed by flash chromatography (1:9 EtOAc/Hexanes) afforded the aldehyde as a clear oil, R_f = 0.20, 0.125 g (61% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, d, *J* = 2.0 Hz), 7.03–7.41 (5H, m), 5.59–5.89 (1H, m), 4.96–5.19 (2H, m), 2.87–3.14 (1H, m), 2.61–2.86 (2H, m), 2.13–2.49 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 170.3, 138.9, 138.5, 134.8, 134.4, 129.2, 129.2, 128.8, 128.7, 126.9, 126.6, 118.2, 117.9, 52.9, 37.2, 35.4, 34.6, 32.9.

(5*S*)-5-benzylocta-1,7-dien-4-ol (42c)



Prepared from **41c** according to the general procedure (A). Light yellow oil, 0.151 g (97% crude yield); ^{1}H NMR (300 MHz, $CDCl_3$) (1:1 mixture of diastereomers) δ 7.09–7.36 (5H, m), 5.65–5.94 (2H, m), 4.95–5.23 (4H, m), 3.66–3.74 (1H, m), 3.63 (1H, dt, *J* = 8.5, 4.0 Hz), 2.72–2.85 (1H, m), 2.53–2.65 (1H, m), 2.31–2.42 (1H, m), 2.12–2.31 (3H, m), 1.96–2.08 (1H, m), 1.81–1.94 (1H, m), 1.61 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 137.6, 137.3, 135.5, 135.5, 129.4, 129.4, 128.5, 128.5, 126.1, 118.3, 118.3, 116.8, 116.6, 71.6, 71.3, 45.0, 39.3, 39.0, 36.5, 35.2, 34.5, 33.4; IR (film) ν 3581, 3441, 3075, 3026, 3001, 2976, 2925, 1639, 1602, 1496, 1454, 1336, 1030, 993, 912 cm^{-1}; MS (EI) *m/z* 175 (10), 157 (100), 115 (11), 91 (72); HRMS (EI) *m/z* ($C_{15}H_{20}O^+$) calcd. 216.1514, found 216.1513.

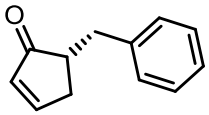
(*S*,*E*)-5-Benzylocta-2,7-dien-4-one (43c)



Prepared from **42c** according to the general procedure (C). Crude product was eluted through a plug of silica (1:4 EtOAc/Hexanes) to give a light yellow oil, 0.0422 g (96% yield); $[\alpha]_D^{24}$ = +39.3 (*c* = 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.33 (5H, m), 6.77 (1H, dq, *J* = 15.5, 7.0 Hz), 6.09 (1H, dq, *J*

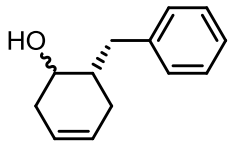
= 15.5, 2.0 Hz), 5.71 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz), 4.94–5.08 (2H, m), 3.09 (1H, tt, *J* = 7.5, 6.0 Hz), 2.88–2.99 (1H, m), 2.70 (1H, dd, *J* = 13.5, 6.5 Hz), 2.34–2.46 (1H, m), 2.15–2.24 (1H, m), 1.83 (3H, dd, *J* = 7.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 143.2, 139.9, 135.6, 131.8, 129.3, 128.6, 126.4, 117.2, 51.0, 37.6, 36.0, 18.5; IR (film) ν 3063, 3028, 2916, 2853, 1693, 1668, 1628, 1441, 918 cm^{-1}; MS (EI) *m/z* 214 (9); 185 (6), 173 (100); HRMS (EI) *m/z* ($C_{15}H_{18}O^+$) calcd. 214.1358, found 214.1358.

(*S*)-5-Benzylcyclopent-2-enone (45c)



Prepared from **43c** according to the general procedure (B). Clear oil, R_f = 0.30 (1:4 EtOAC/Hexanes), 0.0127 g (69% yield); $[\alpha]_D^{26}$ = -111.0 (*c* = 4.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, ddd, *J* = 3.0, 3.0, 3.0 Hz), 7.06–7.37 (5H, m), 6.20 (1H, ddd, *J* = 5.5, 2.0, 2.0 Hz), 3.22 (1H, dd, *J* = 13.0, 3.0 Hz), 2.50–2.81 (3H, m), 2.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 163.9, 139.6, 133.9, 129.1, 128.7, 126.6, 46.5, 37.0, 35.1; IR (film) ν 3062, 3024, 2922, 2851, 1698, 1585, 1494, 1451, 1341, 1171 cm^{-1}; MS (ESI) *m/z* 173 (100); 119 (4), 79 (10), 65 (13); HRMS (ESI) *m/z* ($C_{12}H_{13}O^+$) calcd. 173.0966, found 173.0963.

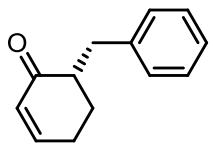
(6*S*)-6-Benzylcyclohex-3-enol (44c)



Prepared from **42c** according to the general procedure (B). Clear oil, R_f = 0.33 (1:4 EtOAc/Hexanes), 0.0224 g (83% yield); Obtained as a mixture of diastereomers. Certain peaks of the minor diastereomer are overlapped by the major diastereomer and cannot be distinguished. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.38 (5H, m), 5.64–5.78 (1H, m), 5.46–5.64 (2H, m), 3.91 (1H, t, *J* = 3.5 Hz), 3.70 (1H, ddd, *J* = 8.5, 7.5, 5.5 Hz), 3.08 (1H, dd, *J* = 13.5, 4.5 Hz), 2.78 (1H, dd, *J* = 13.5, 6.5 Hz), 2.59 (1H, dd, *J* = 13.5, 7.0 Hz), 2.36–2.50 (1H, m), 2.36–2.50 (1H, m), 2.11–2.36 (1H, m), 1.85–2.11 (3H, m), 1.72–1.83 (1H, m), 1.64 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.6, 129.4, 129.4, 128.5, 128.5, 126.8, 126.3, 126.1, 126.1, 124.0, 123.5, 70.9, 67.3, 42.1, 40.1, 38.4, 38.2, 34.2, 34.2, 29.3, 27.2; IR (film) ν 3566, 3371, 3024.87, 2911, 2839, 1495, 1454, 1048 cm^{-1}; MS (EI)

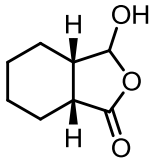
m/z 170 (84), 115 (13), 92 (100), 79 (26), 77 (12); HRMS (EI) *m/z* ($C_{13}H_{16}O^+$) calcd. 188.1201, found 188.1199.

(*S*)-6-Benzylcyclohex-2-enone (46c)[120]



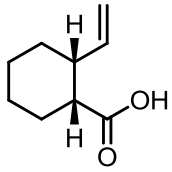
Prepared from **44c** according to the general procedure (C). Clear oil, R_f = 0.70 (1:9 EtOAc/Hexanes), 0.0126 g (70% yield); $[\alpha]_D^{28}$ = +11.6 (*c* = 9.1, $CHCl_3$), lit. $[\alpha]_D^{25}$ = -16.5 (enantiomer, *c* = 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.45 (5H, m), 6.84–7.05 (1H, m), 5.93–6.17 (1H, m), 3.24–3.49 (1H, m), 2.17–2.67 (4H, m), 1.87–2.10 (1H, m), 1.52–1.81 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 150.0, 140.2, 129.8, 129.4, 128.6, 126.3, 48.7, 35.5, 27.3, 25.6; IR (film) ν 3024, 2922, 2857, 1674, 1494, 1451, 1386, 1220, 1123 cm^{-1}; MS (ESI) *m/z* 300 (9), 283 (34), 271 (14), 255 (15), 239 (21), 187 (100), 177 (12), 151 (47); HRMS (ESI) *m/z* ($C_{13}H_{15}O^+$) calcd. 187.1123, found 187.1118.

(3a*S*,7a*R*)-3-Hydroxyhexahydroisobenzofuran-1(3*H*)-one (55)[117]



Prepared according to the literature procedure. Clear oil, 2.84 g (67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (6H, br s), 4.49 (1H, br s), 2.98 (1H, br s), 2.30–2.50 (1H, m), 2.12 (1H, d, *J* = 13.5 Hz), 1.79–1.97 (1H, m), 1.51–1.76 (2H, m), 0.99–1.30 (2H, m).

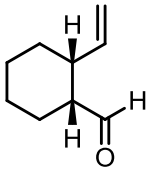
(1*R*,2*R*)-2-Vinylcyclohexanecarboxylic acid (56)[121]



To a solution of methyltriphenylphosphonium bromide (4.74 g, 13.27 mmol) in THF (50 mL) at 0 °C under nitrogen, was added *n*butyllithium (2.46 M, 5.40 mL, 13.28 mmol). The resulting dark red solution was stirred at 0 °C for 35 min at which point **55** (0.690 g, 4.42 mmol) dissolved in THF (5 mL) was transferred by cannula. The reaction turned yellow, and the ice bath was removed and the reaction allowed to stir at room temperature overnight and quenched with saturated sodium bicarbonate solution (12 mL). The product was partitioned between EtOAc (30 mL) and water (50 mL), and the aqueous layer was washed with EtOAc (2 x 30 mL), and these were discarded. The aqueous layer was

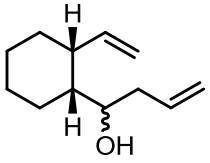
acidified to pH 2, then extracted with ether (3 x 40 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (1:4 EtOAc/Hexanes) gave the carboxylic acid product as a clear oil, R_f = 0.45, 0.608 g (73% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (1H, ddd, *J* = 17.0, 10.5, 8.0 Hz), 4.97–5.17 (2H, m), 2.51–2.78 (2H, m), 1.19–1.92 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 138.4, 116.0, 46.0, 41.3, 30.4, 24.8, 24.4, 22.2.

(1*R*,2*R*)-2-Vinylcyclohexanecarbaldehyde (41d)



To a solution of **56** (0.584 g, 3.79 mmol) in ether (20 mL) cooled to 0 °C was added lithium aluminum hydride (0.162 g, 4.27 mmol). This was stirred overnight under argon at room temperature, and then quenched with a 3M NaOH solution and Rochelle's salt, extracted into EtOAc, dried with $MgSO_4$ and concentrated *in vacuo*. This crude alcohol (**57**) was redissolved in CH_2Cl_2 (20 mL) and DMP (2.001 g, 4.72 mmol) was added. The mixture was stirred for 2.5 h until all starting material was consumed as monitored by TLC analysis then quenched with $Na_2S_2O_3$ (0.45 g, 2.85 mmol) in 10 mL each ether and saturated sodium bicarbonate solution. Extraction into ether followed by flash chromatography (1:4 EtOAc/hexanes) yielded the aldehyde as a clear oil, R_f = 0.78, 0.318 g (64% yield over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, d, *J* = 1.0 Hz), 5.87–6.13 (1H, m), 4.93–5.21 (2H, m), 2.60–2.84 (1H, m), 2.48 (1H, ddd, *J* = 7.5, 4.0, 4.0 Hz), 1.78–1.95 (1H, m), 1.51–1.78 (4H, m), 1.33–1.51 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 139.0, 115.9, 52.3, 40.6, 30.2, 24.0, 23.9, 23.4; IR (film) ν 3077, 2934, 2856, 2672, 1701, 1418, 1259, 916 cm^{-1}.

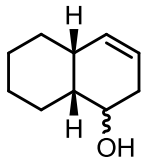
1-((1*R*,2*R*)-2-Vinylcyclohexyl)but-3-en-1-ol (42d)



Prepared from **41d** according to the general procedure (A). Light yellow oil, R_f = (1:19 EtOAc/Hexanes), 0.335 g (87% yield); Obtained as a 5:1 mixture of diastereomers. Certain peaks of the minor diastereomer are overlapped by the major diastereomer and cannot be distinguished. ^{1}H NMR (300 MHz, $CDCl_3$): (Major Isomer) δ 6.07–6.30 (1H, m), 5.71–5.98 (1H, m), 4.96–5.24 (4H, m), 3.29–3.53 (1H, m),

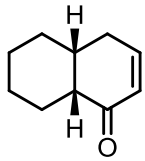
2.26–2.54 (2H, m), 2.00–2.21 (1H, m), 1.14–1.95 (10H, m), (Minor Isomer) δ 2.75 (2H, dd, *J* = 9.0, 4.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 135.5, 118.1, 117.9, 115.9, 73.5, 72.8, 46.0, 46.0, 42.1, 39.8, 39.5, 38.9, 33.7, 32.8, 26.5, 26.5, 24.6, 23.3, 21.4, 21.4; IR (film) ν 3394, 3073, 2925, 2859, 1636, 1448, 1039, 995, 911 cm^{-1}; MS (ESI) *m/z* 181 (39), 163 (42), 149 (8), 139 (100), 121 (4), 107 (5); HRMS (ESI) *m/z* ($C_{12}H_{21}O^+$) calcd. 181.1592, found 181.1589.

(4a*R*,8a*R*)-1,2,4a,5,6,7,8,8a-Octahydronaphthalen-1-ol (44d)



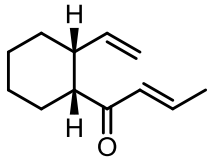
Prepared from **42d** according to the general procedure (B). Clear oil after flash chromatography (1:9 EtOAC/Hexanes), 0.0366 g (83% yield); Obtained as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55–5.65 (1H, m), 5.52–5.54 (2H, m), 5.30–5.41 (1H, m), 3.85–3.99 (1H, m), 2.41–2.61 (1H, m), 2.39 (1H, ddd, *J* = 4.5, 3.0, 1.5 Hz), 2.35 (1H, ddd, *J* = 4.5, 3.0, 1.0 Hz), 2.22–2.34 (1H, m), 1.66–2.06 (3H, m), 1.10–1.65 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 131.3, 125.1, 123.4, 71.1, 68.0, 41.1, 40.5, 36.5, 32.8, 31.8, 31.6, 31.1, 31.0, 25.6, 25.5, 24.2, 24.1, 22.5, 19.8, 14.3; IR (film) ν 3341, 3016, 2925, 2854, 1446, 1046, 1033 cm^{-1}; MS (ESI) 202 (15), 186 (8), 171 (8), 170 (100), 167 (35), 151 (15), 149 (12), 135 (65), 133 (7), 121 (7), 102 (2); HRMS (ESI) *m/z* ($C_{10}H_{20}NO^+$; M + NH_4^+) calcd. 170.1545, found 170.1539.

(4a*R*,8a*R*)-4a,5,6,7,8,8a-Hexahydronaphthalen-1(4*H*)-one (46d)



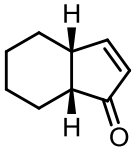
Prepared from **44d** according to the general procedure (C). Clear oil after flash chromatography (1:9 EtOAc/Hexanes), 0.0307 g (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79–7.00 (1H, m), 5.97 (1H, ddd, *J* = 10.0, 2.0, 2.0 Hz), 2.22–2.58 (4H, m), 1.83–2.03 (1H, m), 1.28–1.67 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 148.8, 129.0, 67.3, 48.2, 35.3, 29.0, 25.2, 23.9, 23.6; IR (film) ν 2927, 2853, 1670, 1388, 1254, 1118 cm^{-1}; MS (ESI) *m/z* 151 (100), 65 (19), 61 (8); HRMS (ESI) *m/z* ($C_{10}H_{15}O^+$) calcd. 151.1123, found 151.1120.

(*E*)-1-((1*R*,2*R*)-2-Vinylcyclohexyl)but-2-en-1-one (43d)



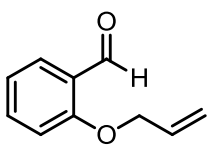
Prepared from **42d** according the general procedure (C). Light yellow oil, 0.0566 g (77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, dq, *J* = 15.5, 7.0 Hz), 6.18 (1H, dq, *J* = 15.5, 1.5 Hz), 5.89 (1H, ddd, *J* = 16.5, 11.01, 8.0 Hz), 4.87–5.03 (2H, m), 2.79 (1H, ddd, *J* = 9.5, 4.0, 4.0 Hz), 2.68 (1H, m), 1.87 (3H, dd, *J* = 7.0, 1.5 Hz), 1.21–1.80 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 141.8, 138.5, 130.7, 115.5, 51.3, 41.6, 31.3, 24.7, 24.1, 22.2, 18.4; IR (film) ν 2931, 2855, 1693, 1631, 1446., 969, 913 cm^{-1}; MS (ESI) 180 (9), 179 (100); HRMS (ESI) *m/z* ($C_{12}H_{19}O^+$) calcd. 179.1436, found 179.1429.

(3a*R*,7a*R*)-3a,4,5,6,7,7a-Hexahydro-1*H*-inden-1-one (45d)[119]



Prepared from **43d** according the general procedure (B). Clear oil after flash chromatography (1:9 EtOAc/Hexanes), 0.0168 g (48% yield; volatile product); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, dd, *J* = 5.5, 3.0 Hz), 6.15 (1H, dd, *J* = 5.5, 1.5 Hz), 2.93–3.03 (1H, m), 2.41 (1H, ddd, *J* = 7.0, 7.0, 7.0 Hz), 1.84–2.02 (2H, m), 1.71 (1H, dddd, *J* = 14.0, 9.5, 7.0, 5.0 Hz), 1.45–1.59 (2H, m), 1.21–1.44 (3H, m), 1.09–1.20 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 168.0, 132.5, 45.6, 41.2, 28.4, 22.8, 21.6, 21.4; IR (film) ν 2932, 2857, 1708, 1447 cm^{-1}; MS (ESI) *m/z* 169 (6) 153 (16), 151 (100), 138 (12), 137 (88), 135 (11); HRMS (ESI) *m/z* ($C_9H_{13}O^+$) calcd. 137.0966, found 137.0964.

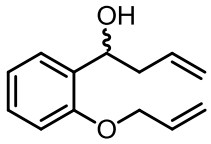
2-(Allyloxy)benzaldehyde (41e)[118]



To a solution of salicaldehyde (0.519 g, 4.25 mmol) in DMF (6 mL) was added potassium carbonate (0.777 g, 5.62 mmol) and allyl bromide (0.54 mL, 6.24 mmol). The mixture was stirred for 24 h under argon then diluted in EtOAc, washed with water and dried with $MgSO_4$. DMF was removed under a stream of air and the crude product was used without further purification; light yellow oil, 0.647 g (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (1H, d, *J* = 1.0 Hz), 7.84 (1H, dd, *J* = 7.5, 2.0 Hz), 7.42–7.64 (1H, m), 6.90–7.14 (2H, m), 6.08 (1H, dddd, *J* = 17.5, 10.5, 5.0, 5.0 Hz), 5.46 (1H, ddt, *J* = 17.0, 1.5, 1.5 Hz), 5.34 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz), 4.66 (2H, ddd, *J* =

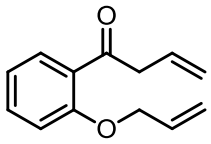
5.0, 1.5, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 161.2, 136.0, 132.6, 128.7, 125.3, 121.1, 118.3, 113.1, 69.4.

1-(2-(Allyloxy)phenyl)but-3-en-1-ol (42e)[122]



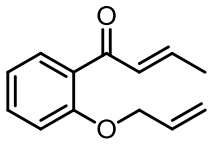
Prepared from **41e** according to the general procedure (A). Light yellow oil, 0.568 g (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mixture of diastereomers) δ 7.30–7.43 (1H, m), 7.09–7.27 (1H, m), 6.90–7.03 (1H, m), 6.84 (1H, dd, *J* = 8.5, 0.5 Hz), 6.04 (1H, dddd, *J* = 17.0, 10.5, 5.0, 5.0 Hz), 5.85 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz), 5.35–5.51 (1H, m), 5.21–5.33 (1H, m), 5.05–5.18 (2H, m), 4.94–5.04 (1H, m), 4.55 (2H, ddd, *J* = 5.0, 1.5, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 135.5, 133.3, 132.4, 128.4, 127.1, 121.1, 117.8, 117.6, 111.9, 69.8, 68.9, 42.2.

1-(2-(Allyloxy)phenyl)but-3-en-1-one (64)



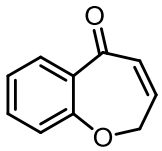
To a solution of **42e** (0.096 g, 0.47 mmol) in CH_2Cl_2 (3 mL) was added DMP (0.242 g, 0.57 mmol) and stirred under argon at room temperature until starting material was fully consumed as monitored by TLC analysis. Excess DMP was quenched with $Na_2S_2O_3$ (0.2 g, 1.26 mmol) in saturated sodium bicarbonate solution (2 mL). Extraction in ether and flash chromatography (1:9 EtOAc/Hexanes) gave the product as a light yellow oil. R_f = 0.30, 0.0806 g (85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, dd, *J* = 7.5, 2.0 Hz), 7.43 (1H, ddd, *J* = 8.5, 7.0, 2.0 Hz), 7.00 (1H, ddd, *J* = 7.5, 1.0, 1.0 Hz), 6.94 (1H, dd, *J* = 8.5, 0.5 Hz), 6.00–6.15 (2H, m), 5.43 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz), 5.33 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz), 5.17 (1H, ddd, *J* = 3.5, 3.0, 1.5 Hz), 5.13 (1H, ddd, *J* = 10.0, 3.0, 1.5 Hz), 4.65 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz), 3.80 (2H, ddd, *J* = 7.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 157.7, 133.6, 132.8, 132.0, 130.8, 128.6, 121.1, 118.5, 118.2, 112.9, 69.6, 48.8 cm^{-1}; MS (ESI) *m/z* 204 (25), 203 (100), 187 (12), 162 (6), 161 (60), 145 (25), 121 (20), 119 (40); HRMS (ESI) *m/z* ($C_{13}H_{15}O_2^+$) calcd. 203.1072, found 203.1067.

(*E*)-1-(2-(Allyloxy)phenyl)but-2-en-1-one (43e)



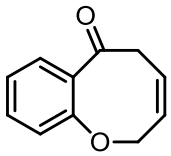
Prepared from **42e** according to the general procedure (C). Light yellow oil, R_f = 0.29 (1:19 EtOAc/Hexanes), 0.0183 g (60 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.58 (2H, m), 6.79–7.07 (3H, m), 6.66–6.79 (1H, m), 6.02 (1H, dddd, *J* = 17.5, 10.5, 5.0, 5.0 Hz), 5.41 (1H, dq, *J* = 17.5, 2.0 Hz), 5.27 (1H, dq, *J* = 10.5, 1.5 Hz), 4.59 (2H, ddd, *J* = 5.0, 1.5, 1.5 Hz), 1.80–2.01 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 157.0, 143.9, 132.9, 132.6, 132.6, 130.4, 129.8, 121.1, 117.6, 113.1, 69.5, 18.5; IR (film) ν 3073, 2981, 2932, 1733, 1650, 1596, 1483, 1448, 1292, 1236, 1161, 991, 755 cm^{-1}; MS (EI) *m/z* 187 (100), 161 (12), 147 (28), 121 (57); HRMS (EI) *m/z* ($C_{13}H_{14}O_2^+$) calcd. 202.0994, found 202.0994.

Benzo[*b*]oxepin-5(2*H*)-one (45e)



Prepared from **43e** according to the general procedure (B). Clear oil, R_f = 0.20 (1:9 EtOAc/Hexanes), 0.0092 g (80% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 8.0, 2.0 Hz), 7.40–7.54 (1H, m), 7.13–7.24 (1H, m), 7.09 (1H, dd, *J* = 8.0, 0.5 Hz), 6.76 (1H, ddd, *J* = 11.5, 5.0, 5.0 Hz), 6.38–6.49 (1H, m), 4.74 (2H, dd, *J* = 5.0, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 159.2, 141.8, 135.0, 134.6, 131.4, 124.1, 121.6, 69.1, 12.2; IR (film) ν 2916, 2846, 1714, 1459, 1376, 1273, 1118 cm^{-1}; MS (ESI) *m/z* 162 (9), 161 (100), 74 (13); HRMS (ESI) *m/z* ($C_{10}H_9O_2^+$) calcd. 161.0602, found 161.0605.

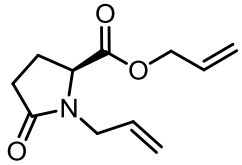
(*Z*)-2*H*-Benzo[*b*]oxocin-6(5*H*)-one (65)



To a solution of **64** (0.027 g, 0.14 mmol) in CH_2Cl_2 (6 mL) was added Hoveyda–Grubbs second-generation catalyst (0.005 g, 0.009 mmol) and stirred at 40 °C under argon for 2 h at which point another 0.003 g (0.004 mmol) of catalyst was added and stirring continued at 40 °C. After a further 4 h, another 0.003 g (0.004 mmol) of catalyst was added and stirred for another 4 hours until mass spectrometric analysis indicated reaction completion. Decolourizing charcoal (0.07 g) was added and the mixture stirred overnight at room temperature. The mixture was filtered and concentrated *in vacuo* to afford the product as a light brown oil, R_f = 0.43 (1:4 EtOAc/Hexanes), 0.0026 g (27% yield); ^{1}H NMR

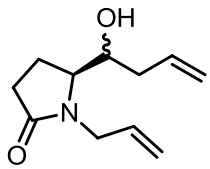
(400 MHz, $CDCl_3$) δ 7.93 (1H, dd, *J* = 8.0, 2.0 Hz), 7.50–7.59 (1H, m), 7.21–7.29 (1H, m), 7.14 (1H, dd, *J* = 8.0, 1.5 Hz), 5.70–5.82 (1H, m), 5.50 (1H, ddddd, *J* = 11.0, 3.0, 3.0, 1.0, 1.0 Hz), 4.81 (2H, dddd, *J* = 3.0, 2.0, 1.0, 1.0 Hz), 3.85 (2H, ddd, *J* = 8.0, 1.0, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 159.6, 135.2, 130.3, 129.8, 128.7, 125.3, 124.5, 123.7, 74.2, 45.3; IR (film) ν 3073, 3024, 2922, 2857, 1677, 1653, 1596, 1475, 1454, 1438, 1290, 1201, 1107, 1064, 1018, 773 cm^{-1}; MS (ESI) *m/z* 176 (10), 175 (100), 173 (14), 159 (30), 157 (14), 121 (40); HRMS (ESI) *m/z* ($C_{11}H_{11}O_2^+$) calcd. 175.0759, found 175.0760.

(*S*)-Allyl 1-allyl-5-oxopyrrolidine-2-carboxylate (63)



To a solution of L-pyroglutamic acid (1.318 g, 10.21 mmol) in DMSO (40 mL) under argon was added sodium hydride (60% suspension in mineral oil, 0.858 g, 21.5 mmol) portion-wise over 10 minutes and stirred for 1 h. Allyl bromide (2.20 mL, 25.4 mmol) was added and the mixture was stirred at room temperature for 6H, then quenched with methanol and placed under a stream of air overnight to remove most of the DMSO. Extraction into EtOAc followed by flash chromatography (3:1 EtOAc/Hexanes) afforded the product as a clear oil, R_f = 0.50, 1.30 g (61 % yield); $[\alpha]_D^{27}$ = +19.6 (*c* = 4.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.83–6.00 (1H, m), 5.63–5.79 (1H, m), 5.25–5.40 (2H, m), 5.11–5.23 (2H, m), 4.60–4.69 (2H, m), 4.36 (1H, dddd, *J* = 15.5, 5.5, 1.5, 1.5 Hz), 4.15–4.24 (1H, m), 3.55 (1H, dd, *J* = 15.0, 7.5 Hz), 2.25–2.62 (3H, m), 2.05–2.17 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 171.8, 132.2, 131.6, 119.5, 119.0, 66.2, 59.2, 44.7, 29.7, 23.1; IR (film) ν 3085, 2932, 1741, 1694, 1646, 1446, 1411, 1275, 1233, 1184, 1039, 985, 933 cm^{-1}; MS (ESI) 211 (9), 210 (100); HRMS (ESI) *m/z* ($C_{11}H_{16}NO_3^+$) calcd. 210.1130, found 210.1137.

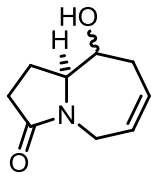
(*S*)-1-Allyl-5-((*S*)-1-hydroxybut-3-en-1-yl)pyrrolidin-2-one (42f)



To a solution of **63** (1.27 g, 6.08 mmol) in THF (19 mL) was added sodium borohydride (1.35 g, 35.8 mmol) in absolute ethanol (6.5 mL) and stirred under argon at room temperature overnight, then quenched with 3 M HCl and saturated Rochelle's salt. The crude alcohol was extracted into chloroform,

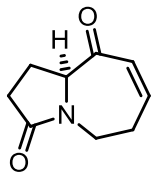
dried and concentrated *in vacuo*, then redissolved in CH_2Cl_2 (24 mL). DMP (3.11 g, 7.35 mmol) was added and stirred under argon until all starting material had been consumed as monitored by mass spectrometry, and then quenched with $Na_2S_2O_3$ (0.76 g, 4.8 mmol) in saturated sodium bicarbonate. The crude aldehyde (**41f**) was extracted into CH_2Cl_2, dried and concentrated *in vacuo*, then redissolved in CH_2Cl_2 and used according to general procedure (A). Flash chromatography (EtOAc) afforded the pure homoallylic alcohol as a clear oil, R_f = 0.66, 0.609 g (51% yield over 3 steps); Obtained as a 3:1 mixture of diastereomers. Certain peaks of the minor diastereomer are overlapped by the major diastereomer and cannot be distinguished. ^{1}H NMR (400 MHz, $CDCl_3$) (Major Isomer) δ 5.70–5.89 (2H, m), 5.10–5.29 (4H, m), 4.21–4.34 (1H, m), 3.56–3.87 (3H, m), 2.22–2.55 (4H, m), 2.02–2.20 (3H, m), 1.83–2.00 (1H, m), (Minor Isomer) δ = 3.92–3.99 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 175.8, 134.3, 134.0, 133.4, 133.1, 119.4, 118.5, 118.3, 117.8, 72.4, 68.6, 61.6, 45.2, 43.6, 37.6, 37.1, 30.7, 30.4, 20.8, 17.8; IR (film) ν 3379, 3078, 2978, 2930, 1670, 1455, 1417, 1191, 1065, 995, 918 cm^{-1}; MS (ESI) *m/z* 196 (100), 178 (3), 151 (7); HRMS (ESI) *m/z* ($C_{11}H_{18}NO_2^+$) calcd. 196.1337, found 196.1330.

(9a*S*)-9-Hydroxy-5,8,9,9a-tetrahydro-1*H*-pyrrolo[1,2-a]azepin-3(2*H*)-one (44f)



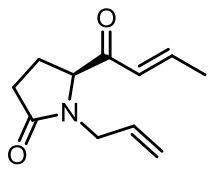
Prepared from **42f** according to general procedure (B). The product was very water soluble and had to be extracted with numerous washes of CH_2Cl_2; Clear oil, R_f = 0.26 (1:19 MeOH/EtOAc), 0.0201 g (82 % yield); Obtained as a 1:1 mixture of diastereomers. Certain peaks of the minor diastereomer are overlapped by the major diastereomer and cannot be distinguished. ^{1}H NMR (300 MHz, $CDCl_3$) (Major isomer) δ 5.83–6.10 (1H, m), 5.55–5.78 (1H, m), 4.45–4.70 (1H, m), 3.94 (1H, br s), 3.82 (1H, ddd, *J* = 8.5, 4.0, 2.0 Hz), 3.26–3.47 (1H, m), 1.66–2.81 (7H, m), (Minor isomer) δ = 3.70 (1H, ddd, *J* = 7.5, 5.5, 5.5 Hz), 3.61 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 174.5, 130.4, 130.2, 127.8, 126.6, 72.4, 70.4, 67.2, 66.0, 40.7, 40.4, 33.7, 33.1, 30.1, 29.9, 22.7, 21.7; IR (film) ν 3371, 3027, 2986, 1663, 1459, 1420, 1262, 1189, 1076, 829, 656 cm^{-1}; MS (EI) *m/z* 181 (32); 167 (100), 84 (62); HRMS (EI) *m/z* ($C_9H_{13}NO_2^+$) calcd. 167.0946, found 167.0942.

(*S*)-5,6-Dihydro-1*H*-pyrrolo[1,2-a]azepine-3,9(2*H*,9*aH*)-dione (46f)



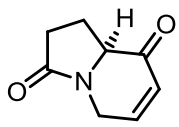
Prepared from **44f** according to the general procedure (C). Clear oil, R_f = 0.37 (1:19 MeOH/EtOAc), 0.0060 g (55% yield); $[\alpha]_D^{25}$ = -22.5 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, ddd, *J* = 12.5, 4.5, 4.5 Hz), 6.07 (1H, ddd, *J* = 12.5, 2.0, 2.0 Hz), 4.22–4.35 (1H, m), 4.16 (1H, ddd, *J* = 14.0, 4.5, 4.5 Hz), 3.14 (1H, ddd, *J* = 4.0, 10.5, 3.5 Hz), 2.75–2.93 (1H, m), 2.49–2.62 (1H, m), 2.32–2.48 (3H, m), 2.07–2.25 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 174.9, 145.7, 130.0, 68.1, 40.6, 31.8, 30.2, 23.3; IR (film) ν 2947, 2846, 1771, 1696, 1400, 1357, 1247, 1161, 819 cm^{-1}; MS (ESI) *m/z* 198.1 (92), 166.1 (100); HRMS (ESI) *m/z* ($C_9H_{12}NO_2^+$) calcd. 166.0868, found 166.0887.

(*S*,*E*)-1-Allyl-5-(but-2-enoyl)pyrrolidin-2-one (43f)



Prepared from **42f** according to the general procedure (C). Clear oil, R_f = 0.23 (EtOAc), 0.0599 g (48 % yield); $[\alpha]_D^{25}$ = 56.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, dq, *J* = 15.5, 7.0 Hz), 6.20 (1H, dq, *J* = 15.5, 1.5 Hz), 5.69 (1H, dddd, *J* = 17.0, 10.0, 8.0, 5.0 Hz), 5.07–5.20 (2H, m), 4.38–4.49 (2H, m), 3.38 (1H, dd, *J* = 15.0, 8.0 Hz), 2.25–2.49 (3H, m), 1.95 (3H, dd, *J* = 7.0, 1.5 Hz), 1.85–1.93 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 175.3, 145.9, 132.4, 127.7, 118.9, 63.2, 44.6, 29.7, 22.5, 18.8; IR (film) ν 3082, 2933, 1693, 1631, 1444, 1411, 1278, 1227, 1192, 1129, 1082, 972, 926 cm^{-1}; MS (ESI) *m/z* 195 (16), 194 (100), 177 (7), 109 (4); HRMS (ESI) *m/z* ($C_{11}H_{16}NO_2^+$) calcd. 194.1181, found 194.1177.

(*S*)-1,8a-Dihydroindolizine-3,8(2*H*,5*H*)-dione (45f)

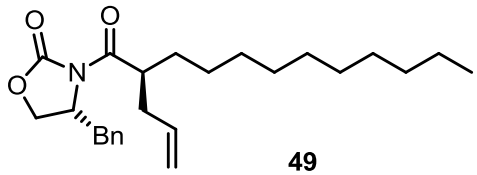


Prepared from **43f** according to the general procedure (B). Viscous clear oil, R_f = 0.29 (1:19 MeOH/EtOAc), 0.0327 g (63 % yield); $[\alpha]_D^{24}$ = -98.3 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, ddd, *J* = 10.5, 4.5, 2.0 Hz), 6.19 (1H, ddd, *J* = 10.5, 3.0, 2.0 Hz), 4.72 (1H, ddd, *J* = 20.5, 4.5, 2.0 Hz), 4.07–4.20 (1H, m), 3.73–3.88 (1H, m), 2.20–2.58 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 174.4, 146.0, 127.9, 61.2, 40.4, 29.9, 20.6; IR (film) ν 3053, 2958, 2829, 1686, 1619, 1415, 1378, 1261, 1196

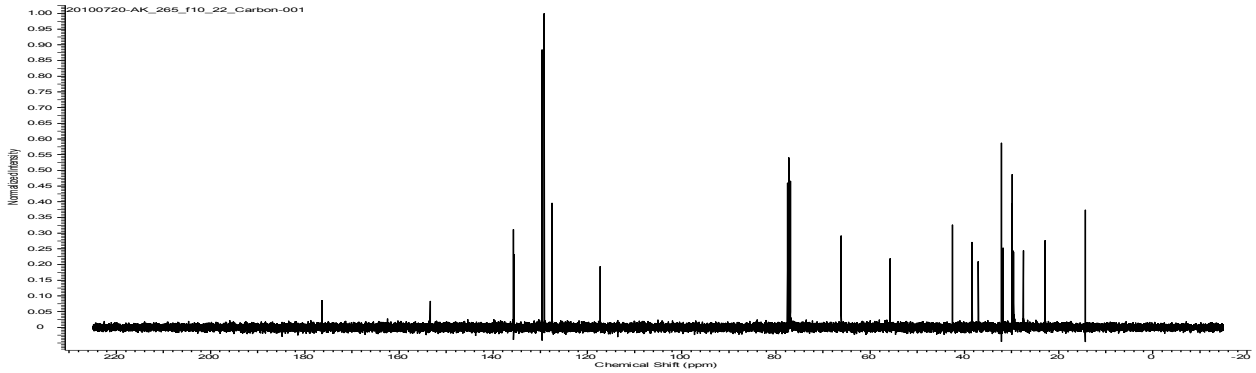
cm^{-1}; MS (ESI) *m/z* 168 (74) 152 (100), 138 (10); HRMS (ESI) *m/z* ($C_8H_{10}NO_2^+$) calcd. 152.0706, found 152.0712.

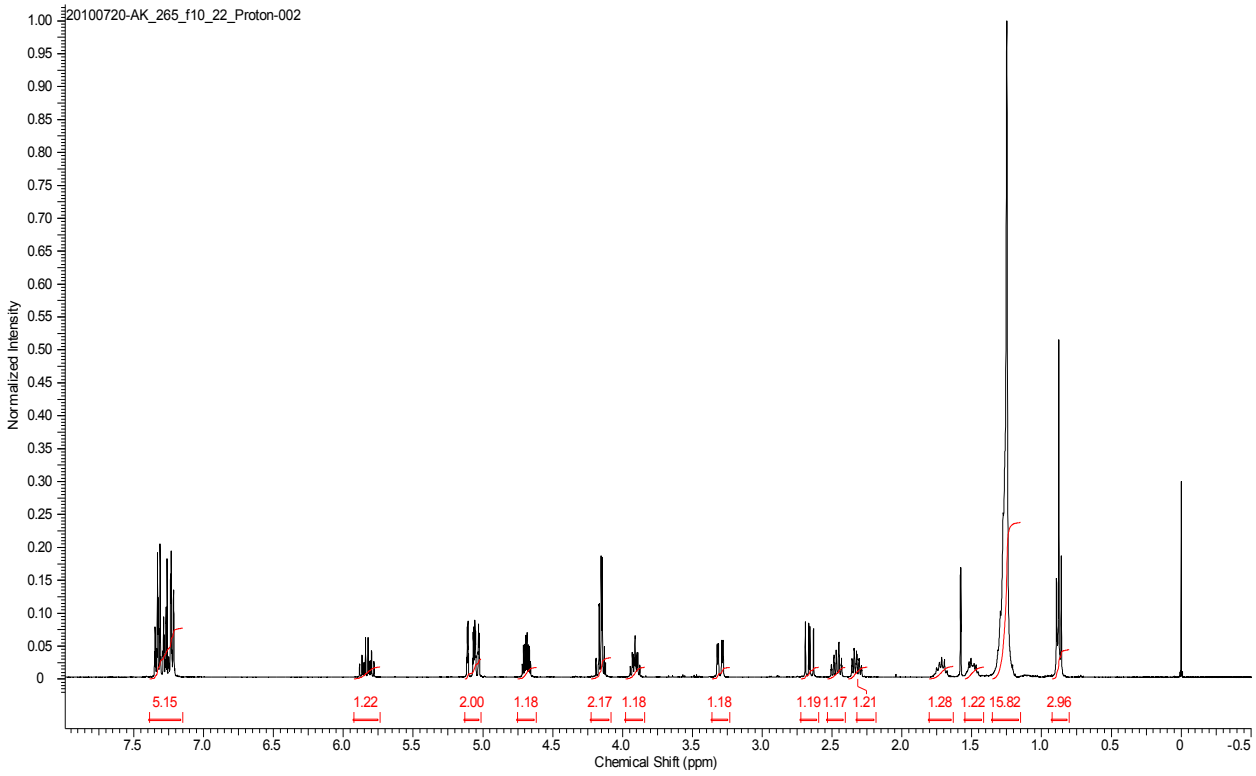
Appendix

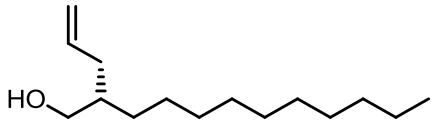
Selected ^{1}H NMR and ^{13}C NMR Spectra



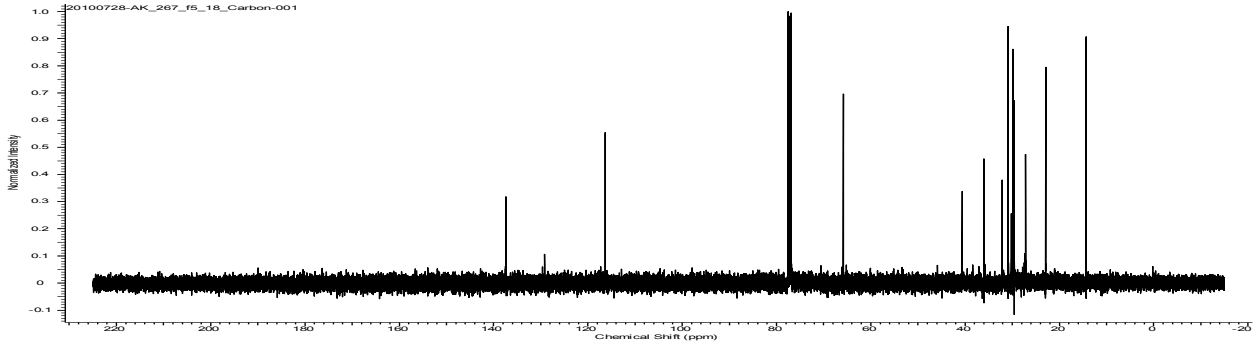
49

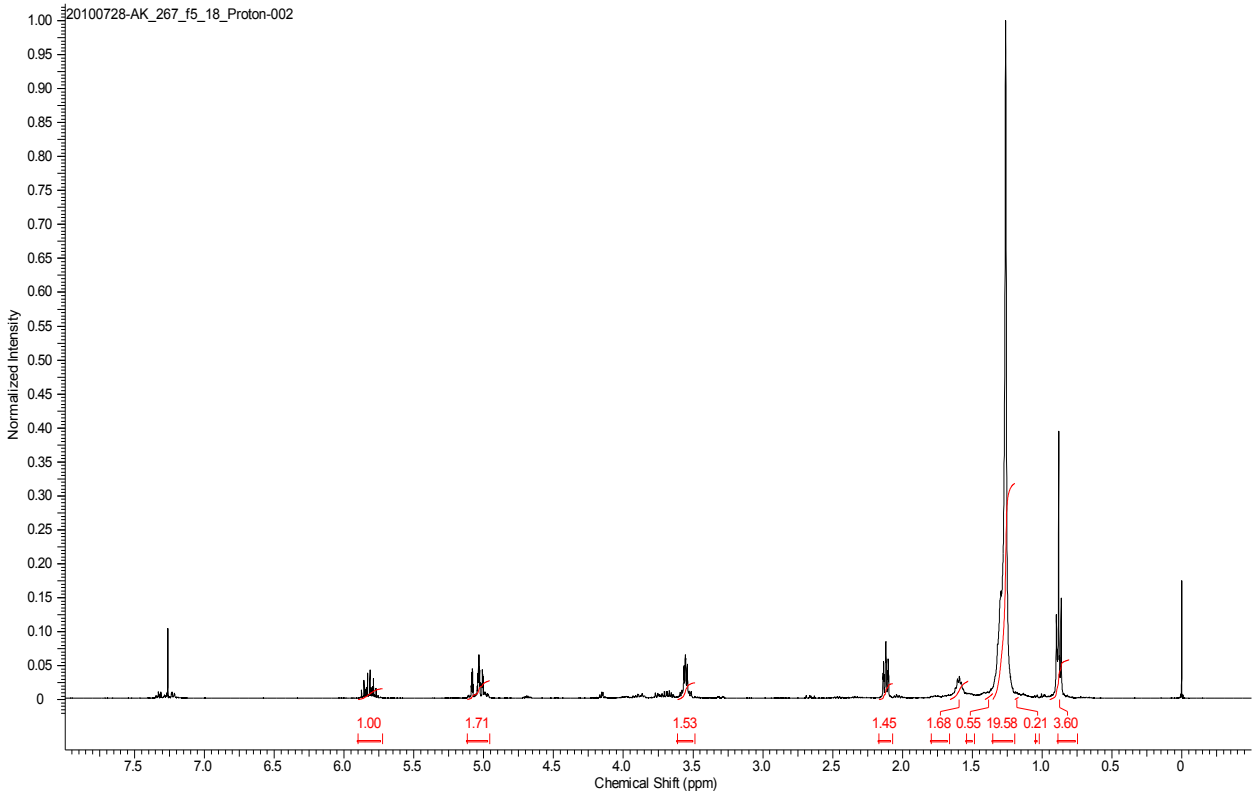


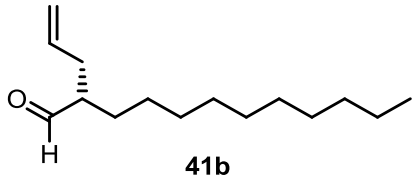



HO

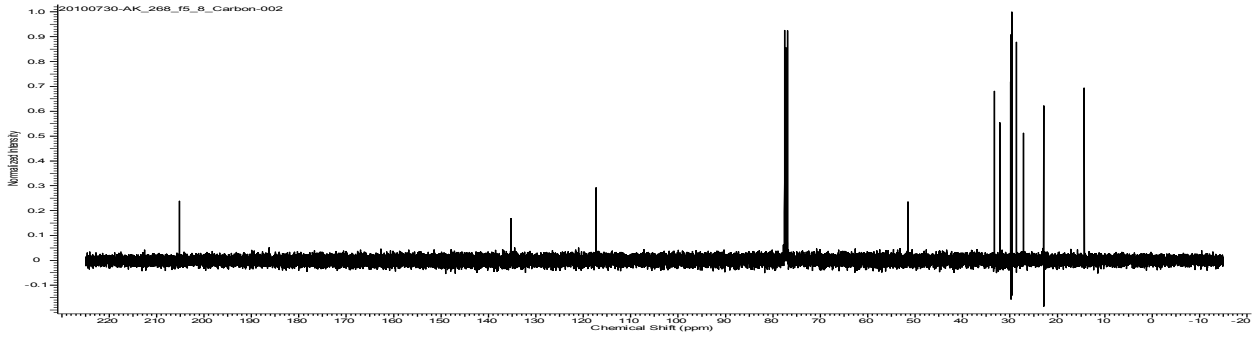
50

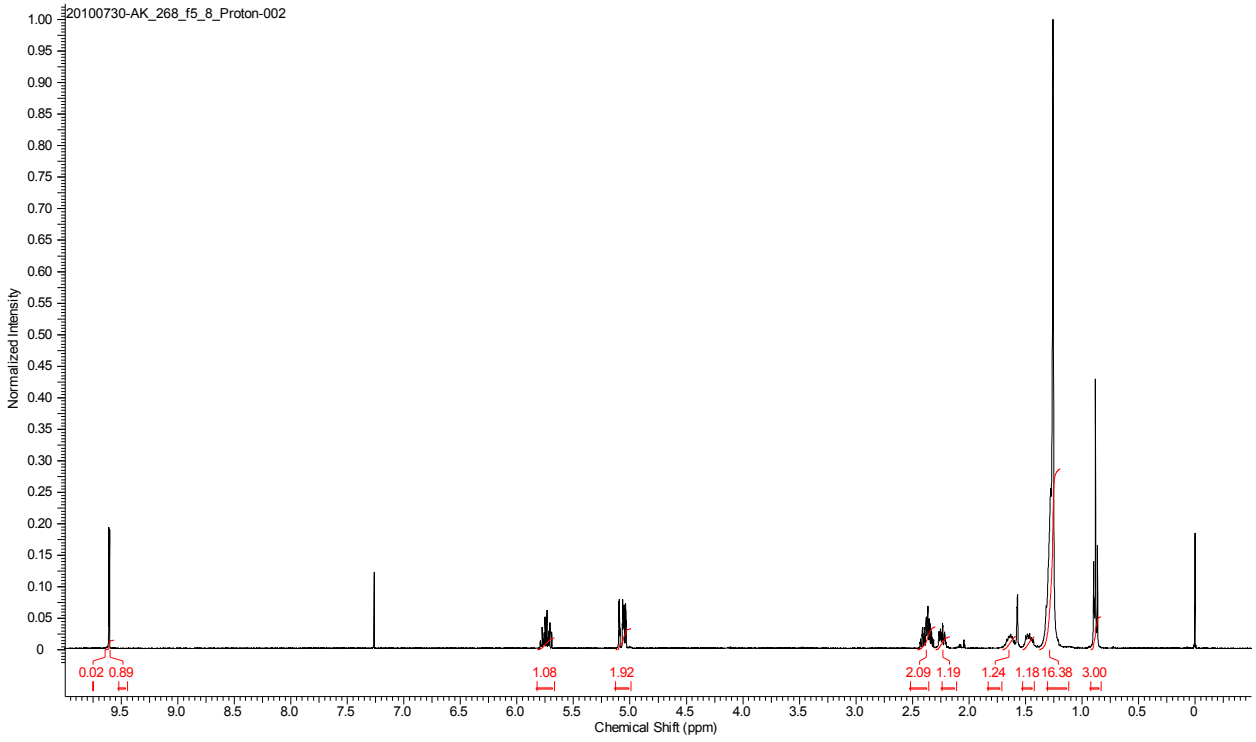

20100728-AK_267_f5_18_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

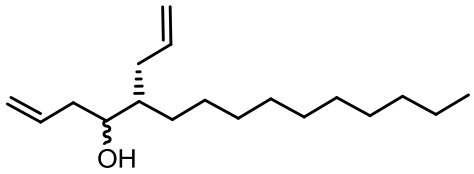

20100728-AK_267_f5_18_Proton-002
Normalized Intensity
1.00
1.71
1.53
1.45
1.68
0.55
19.58
0.21
3.60
Chemical Shift (ppm)


O
H

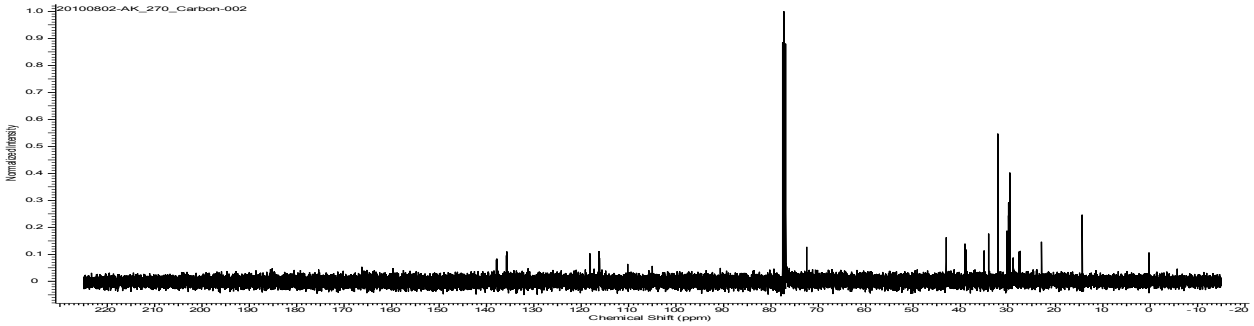
41b

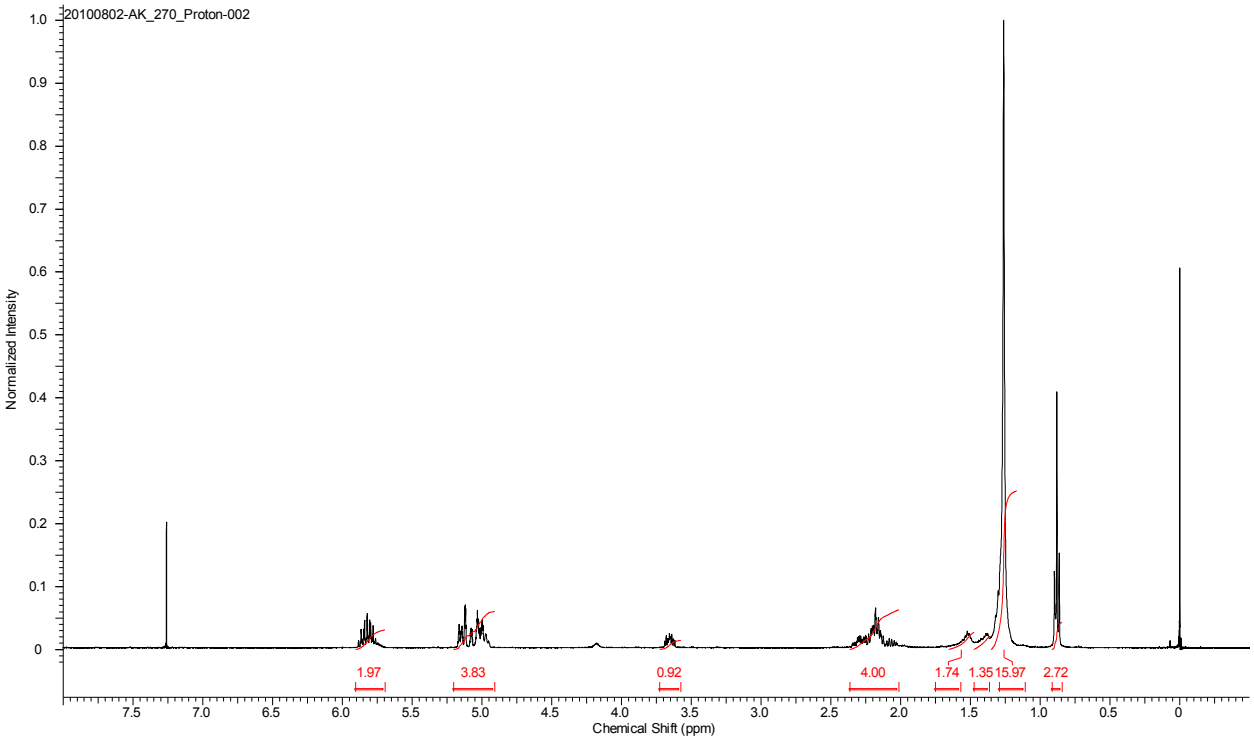

20100730-AK_268_f5_8_Carbon-002
Normalized Intensity
Chemical Shift (ppm)

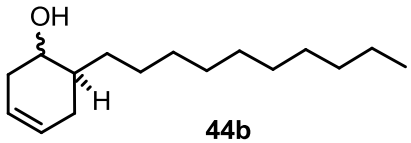

20100730-AK_268_f5_8_Proton-002
Normalized Intensity
0.02 0.89
1.08
1.92
2.09 1.19
1.24
1.18 16.38
3.00
Chemical Shift (ppm)


OH

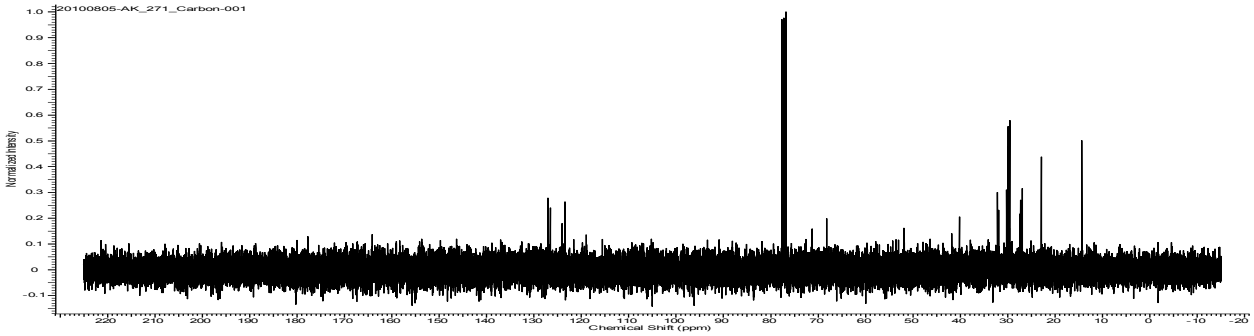
42b

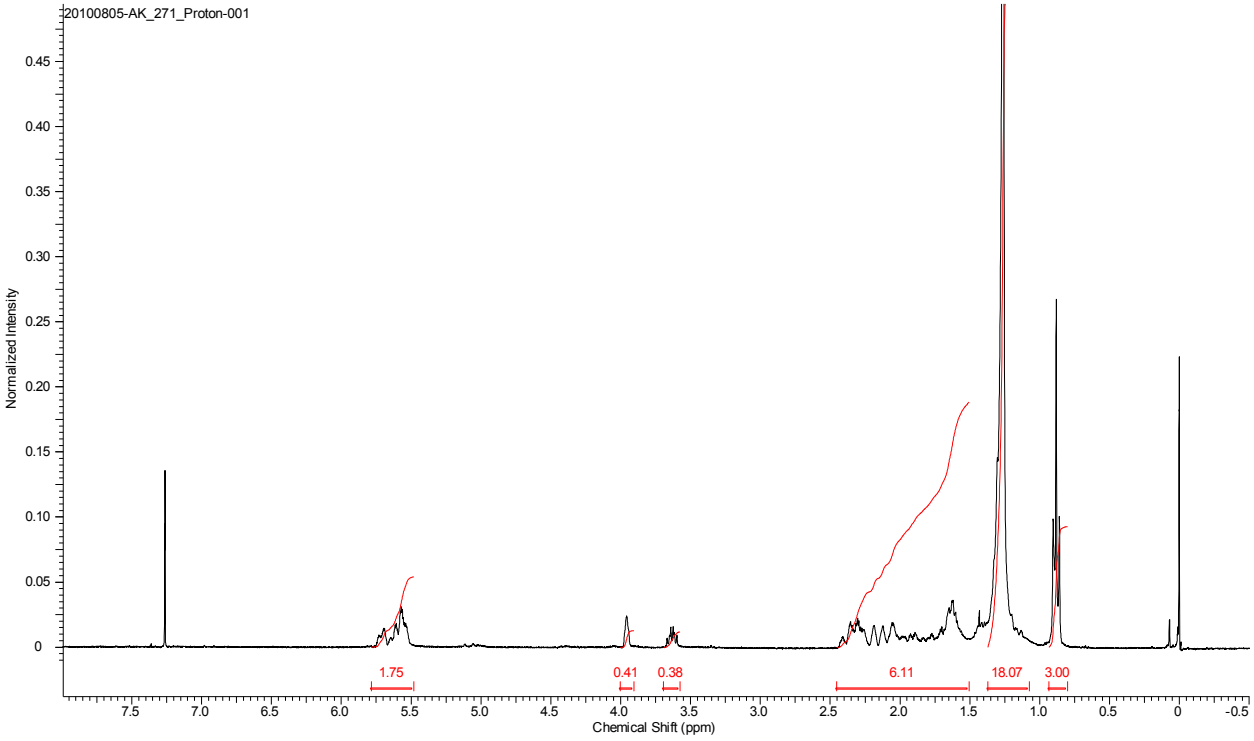

20100802-AK_270_Carbon-002
Normalized Intensity
Chemical Shift (ppm)

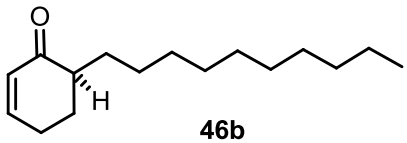

20100802-AK_270_Proton-002
Normalized Intensity
1.97
3.83
0.92
4.00
1.74
1.35
15.97
2.72
Chemical Shift (ppm)


OH
H

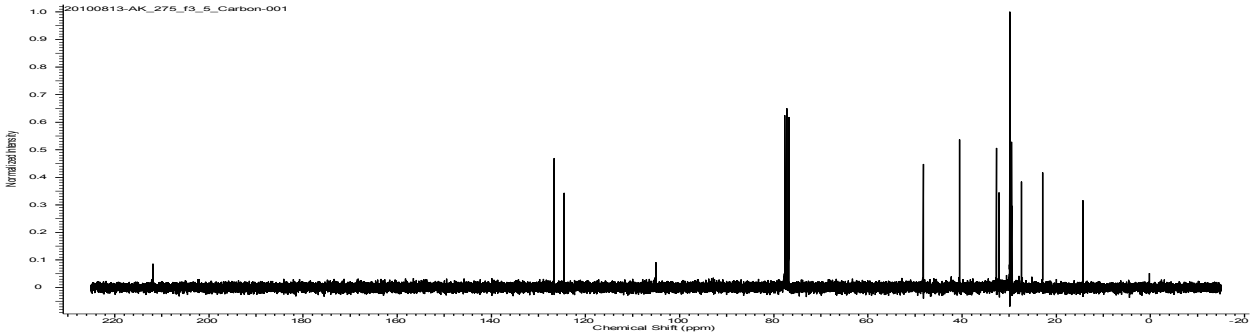
44b

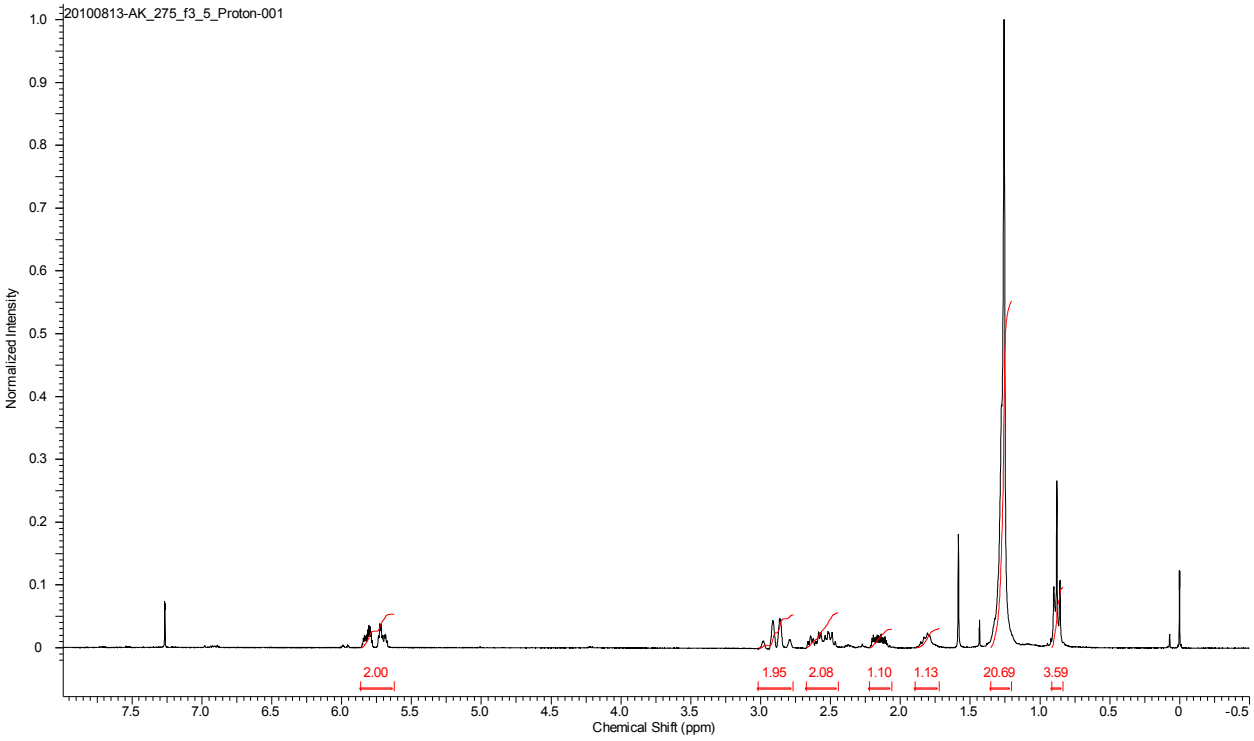

20100805-AK_271_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

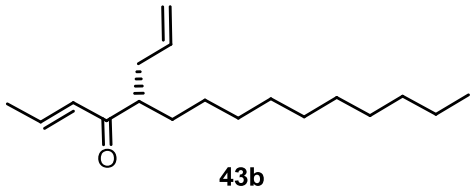

20100805-AK_271_Proton-001
Normalized Intensity
1.75
0.41
0.38
6.11
18.07
3.00
Chemical Shift (ppm)


O
H

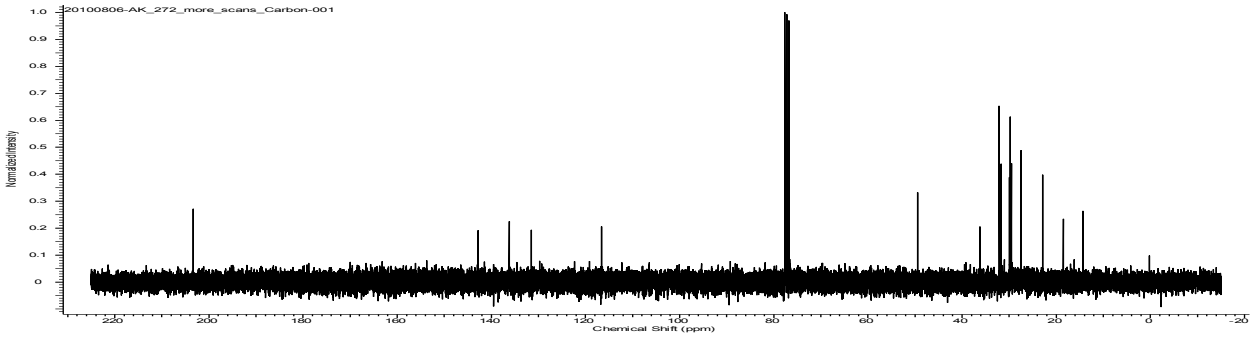
46b

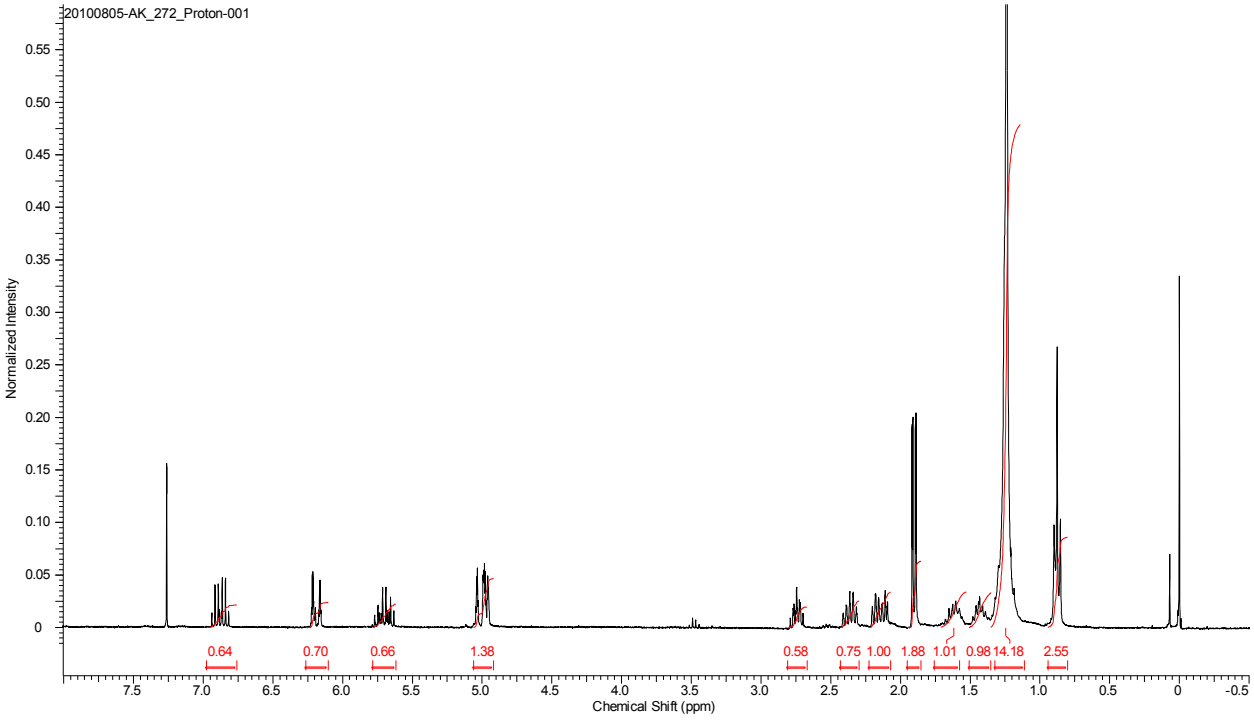

20100813-AK_275_f3_5_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

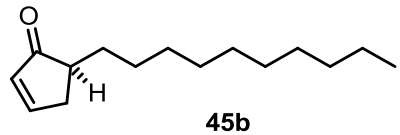

20100813-AK_275_f3_5_Proton-001
Normalized Intensity
2.00
1.95
2.08
1.10
1.13
20.69
3.59
Chemical Shift (ppm)



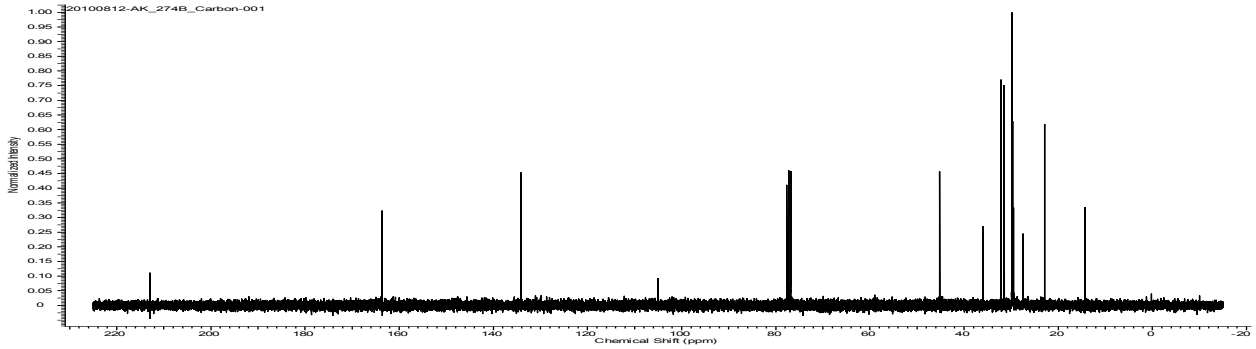
43b

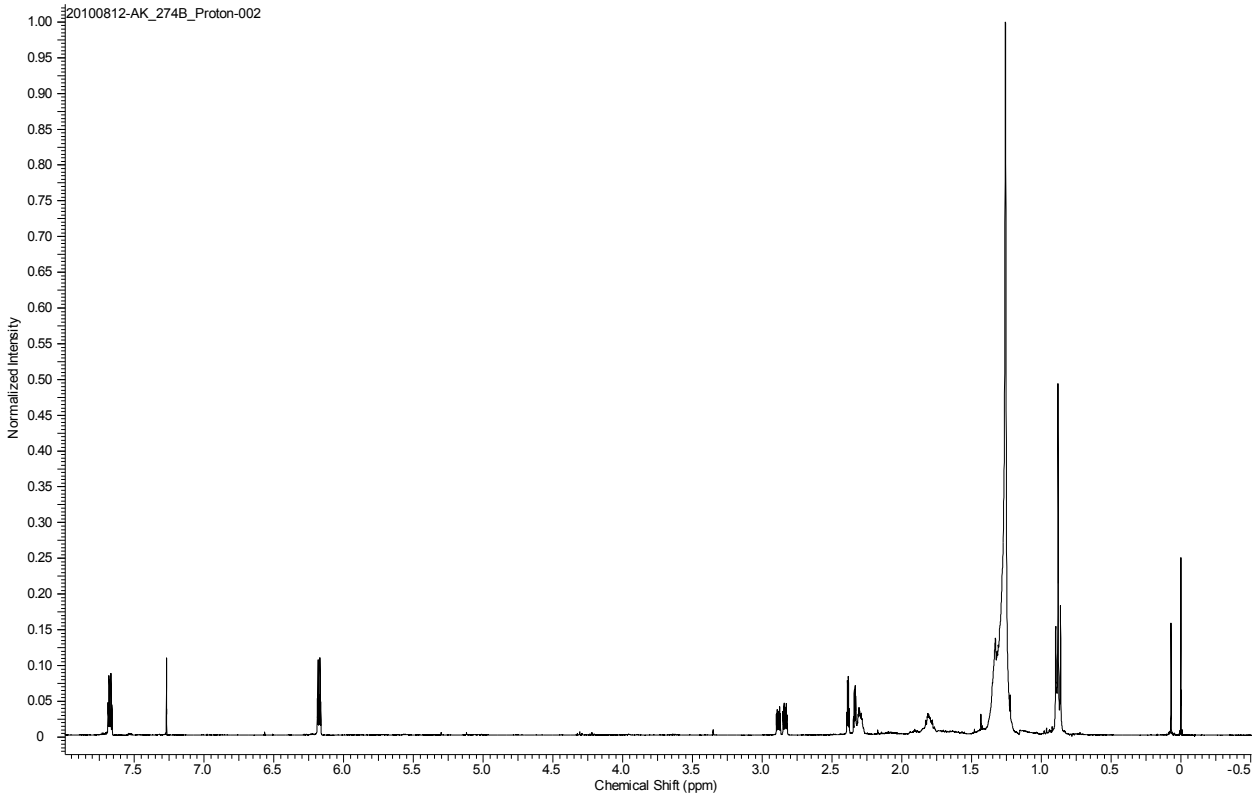

20100806-AK_272_more_scans_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

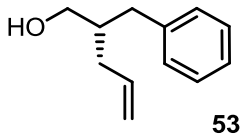

20100805-AK_272_Proton-001
Normalized Intensity
0.64
0.70
0.66
1.38
0.58
0.75
1.00
1.88
1.01
0.98
14.18
2.55
Chemical Shift (ppm)


O
H

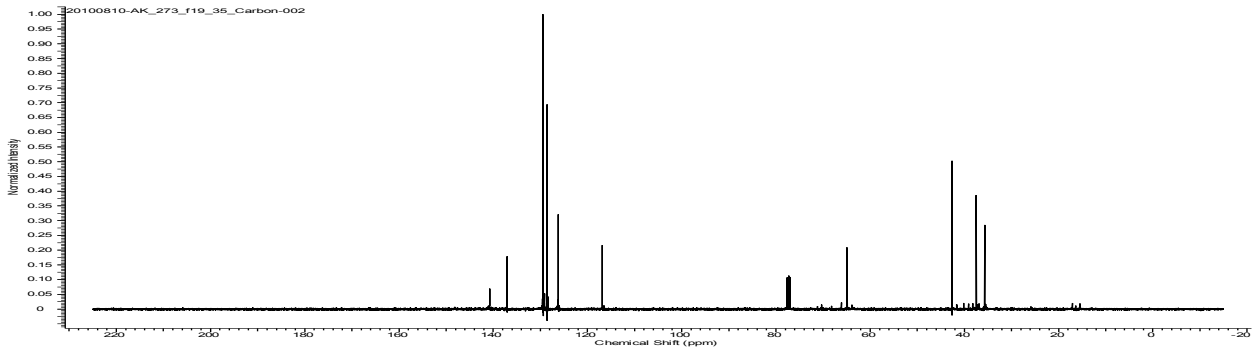
45b

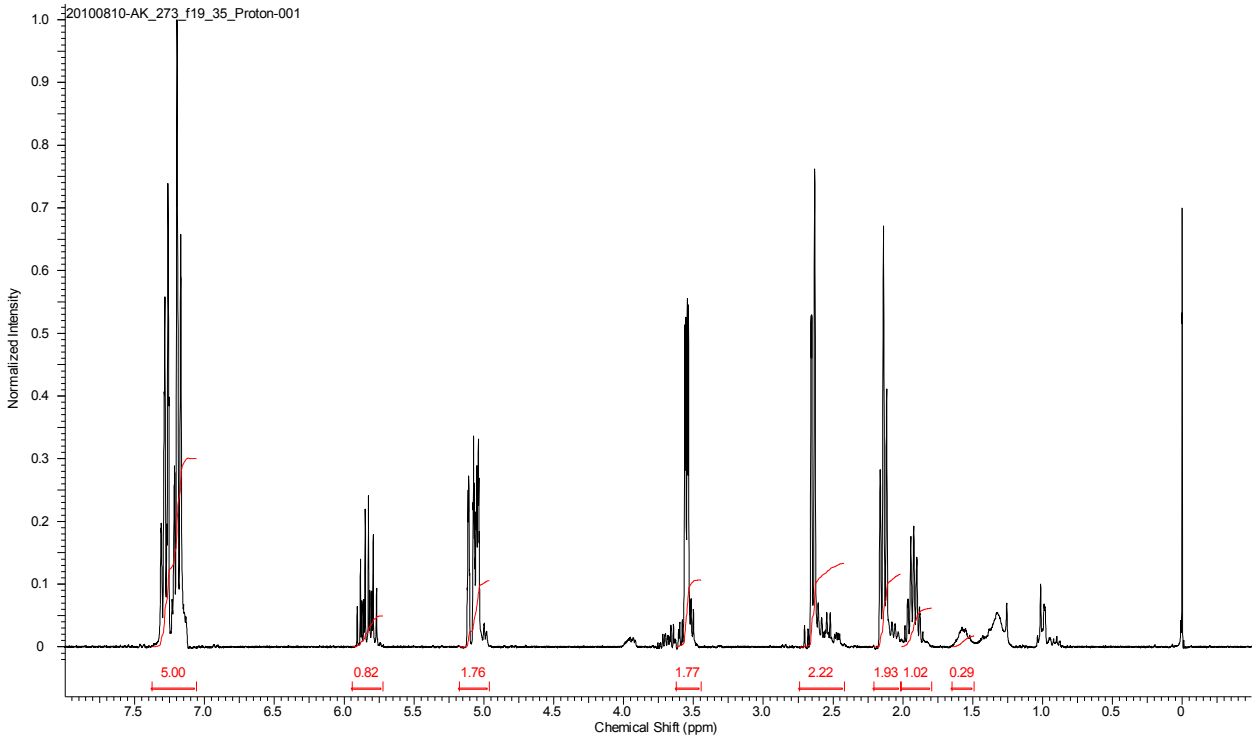

20100812-AK_274B_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

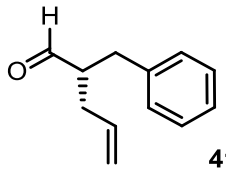

20100812-AK_274B_Proton-002
Normalized Intensity
Chemical Shift (ppm)


HO

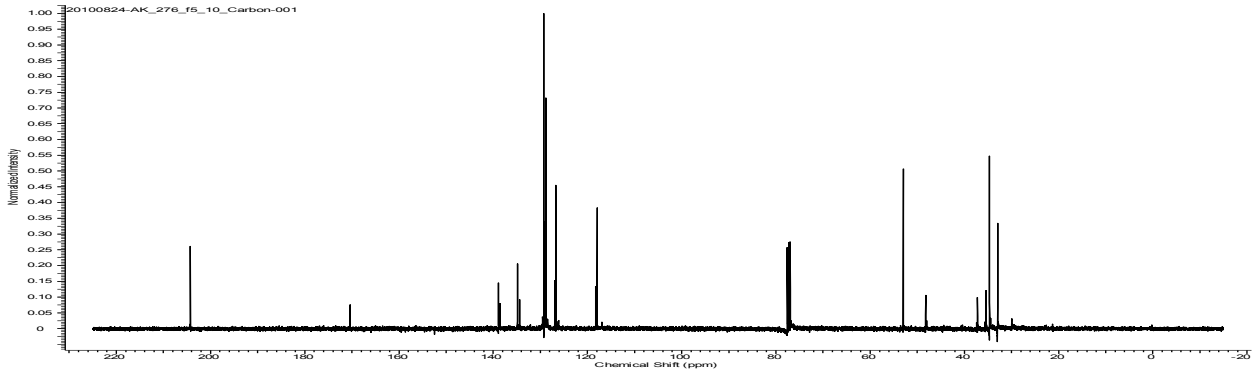
53

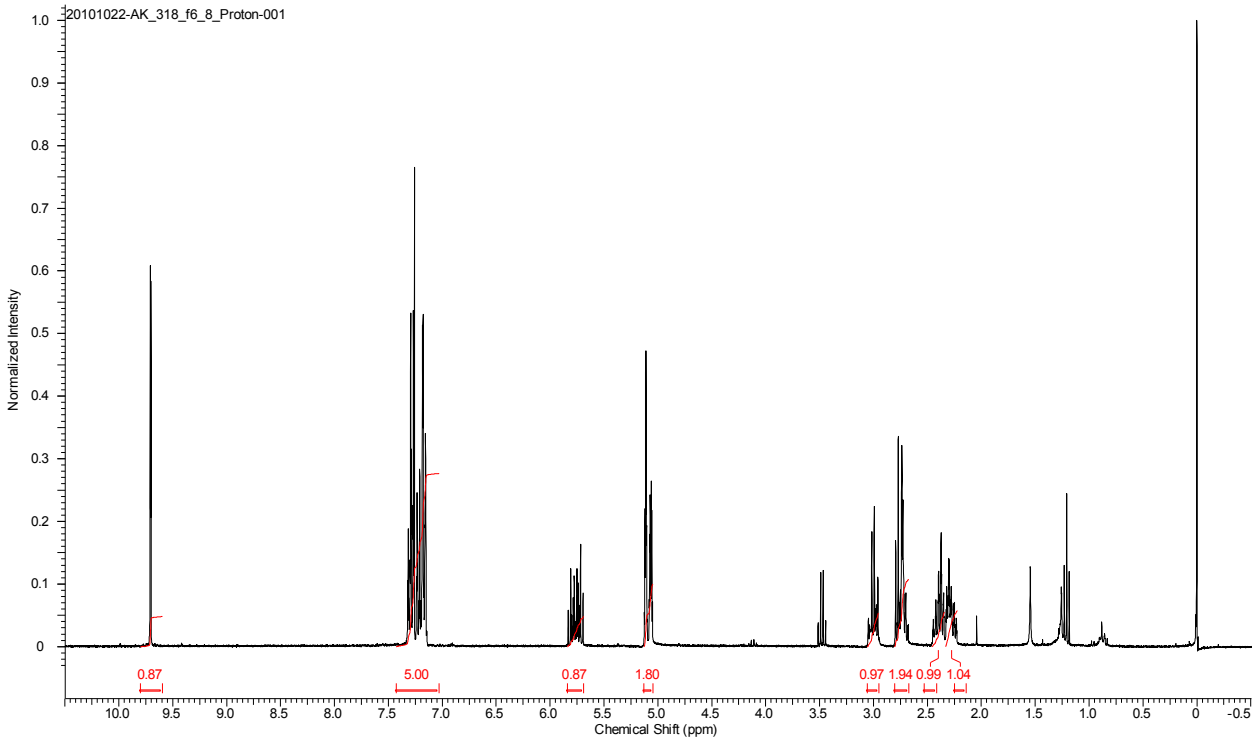

20100810-AK_273_f19_35_Carbon-002
Normalized Intensity
Chemical Shift (ppm)

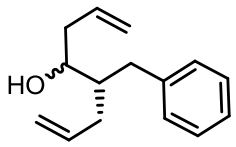

20100810-AK_273_f19_35_Proton-001
Normalized Intensity
5.00
0.82
1.76
1.77
2.22
1.93
1.02
0.29
Chemical Shift (ppm)


H
O

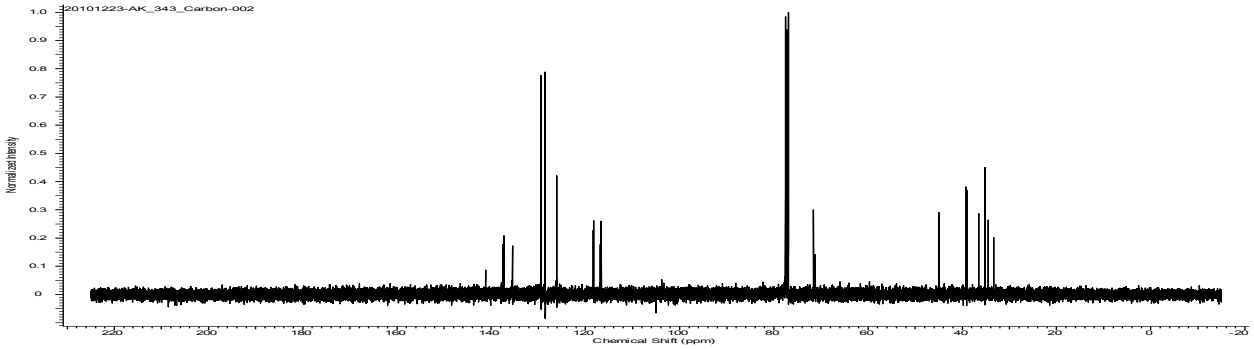
41c

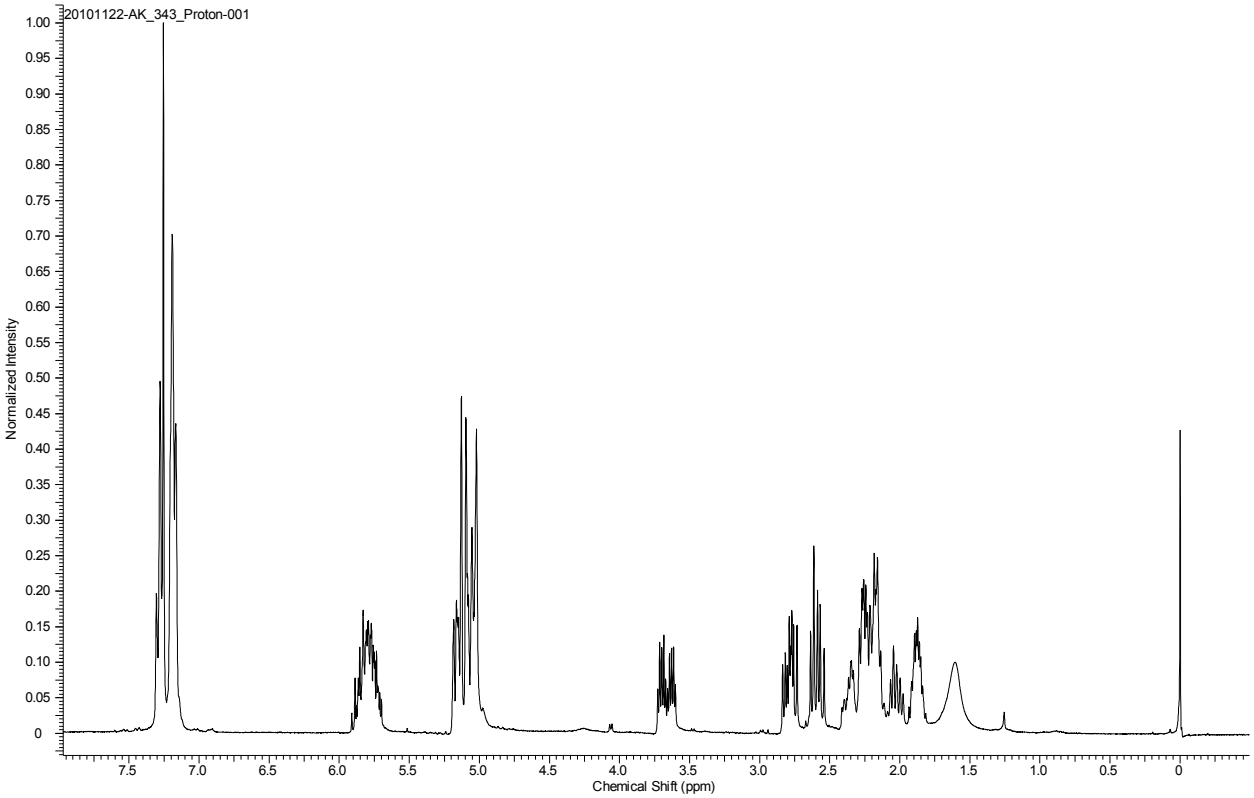

20100824-AK_276_f5_10_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

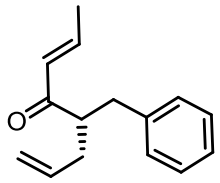

20101022-AK_318_f6_8_Proton-001
Normalized Intensity
0.87
5.00
0.87
1.80
0.97
1.94
0.99
1.04
Chemical Shift (ppm)


HO

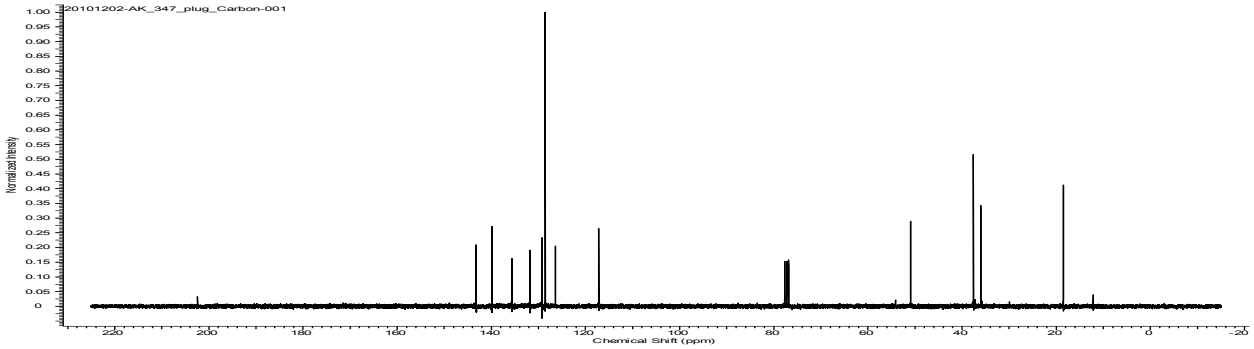
42c

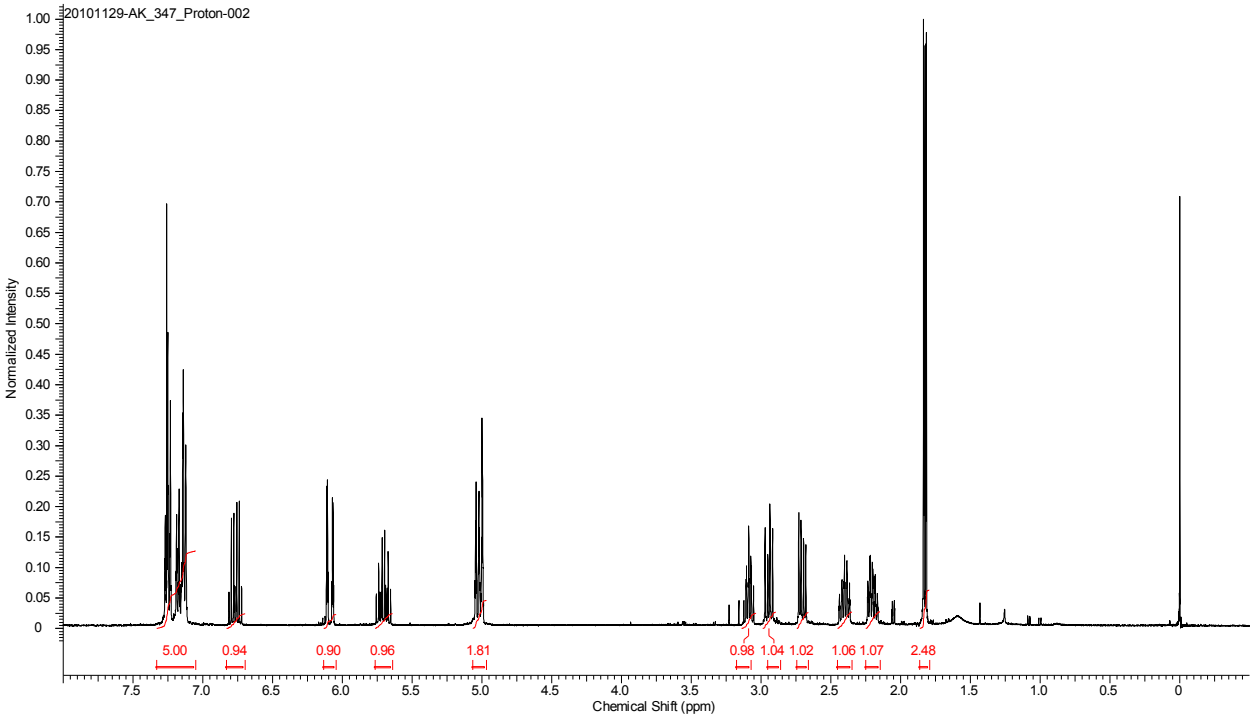

20101223-AK_343_Carbon-002
Normalized Intensity
Chemical Shift (ppm)

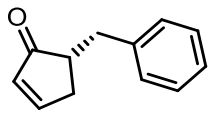

20101122-AK_343_Proton-001
Normalized Intensity
Chemical Shift (ppm)



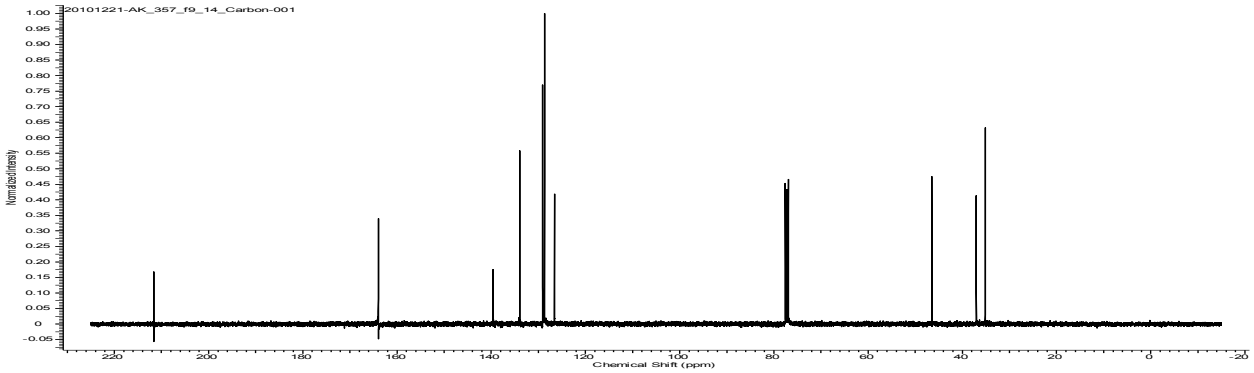
43c

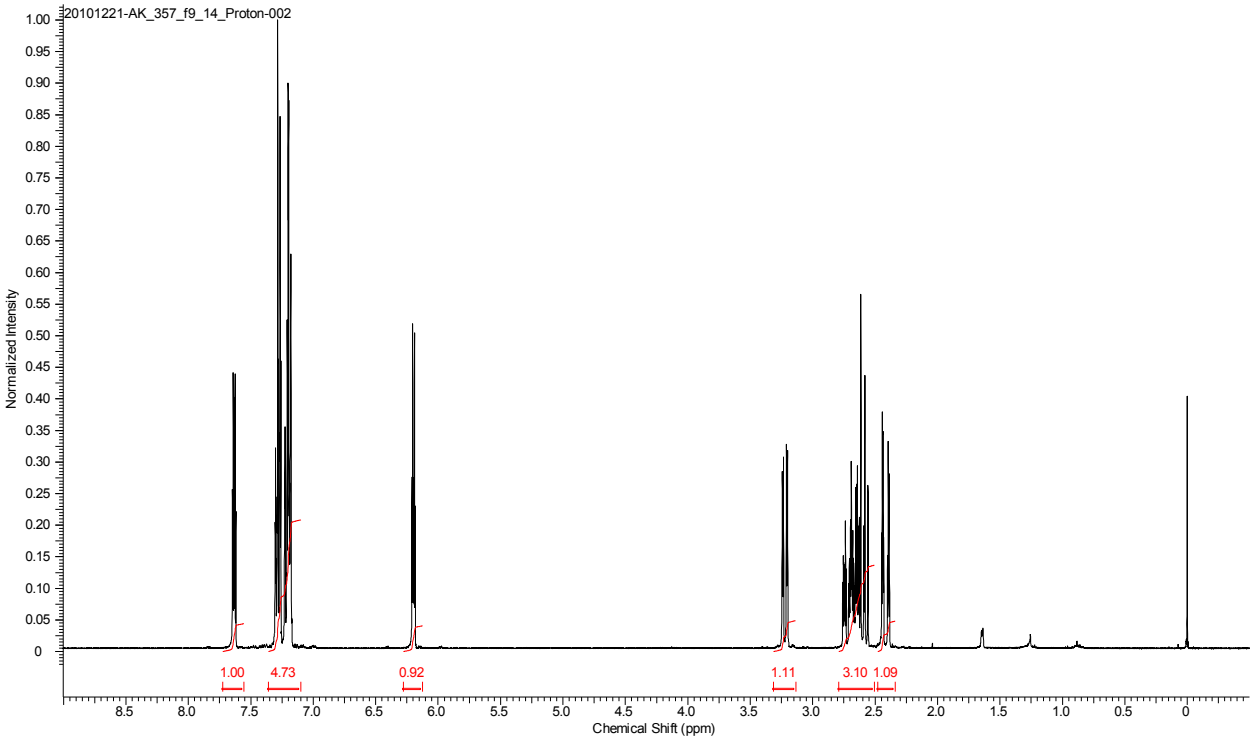

20101202-AK_347_plug_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

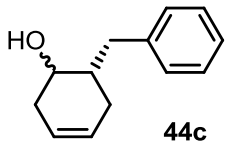

20101129-AK_347_Proton-002
Normalized Intensity
5.00
0.94
0.90
0.96
1.81
0.98
1.04
1.02
1.06
1.07
2.48
Chemical Shift (ppm)



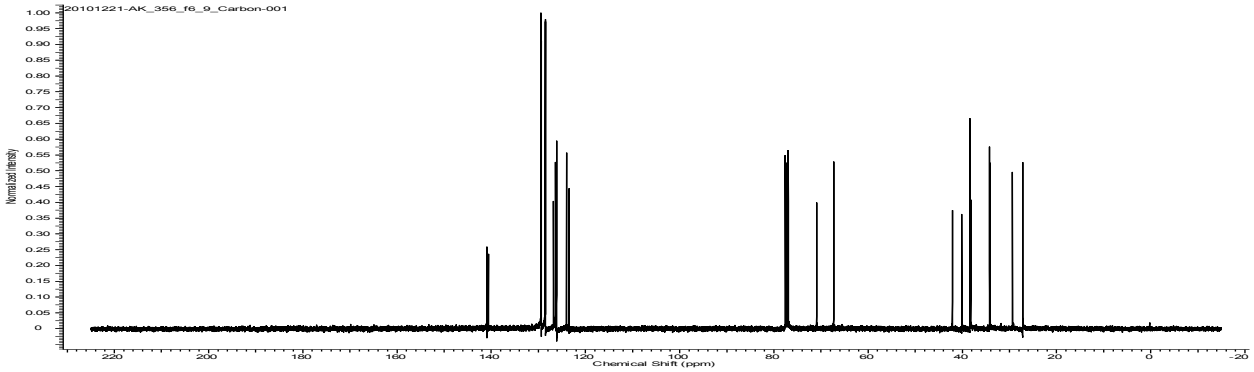
45c

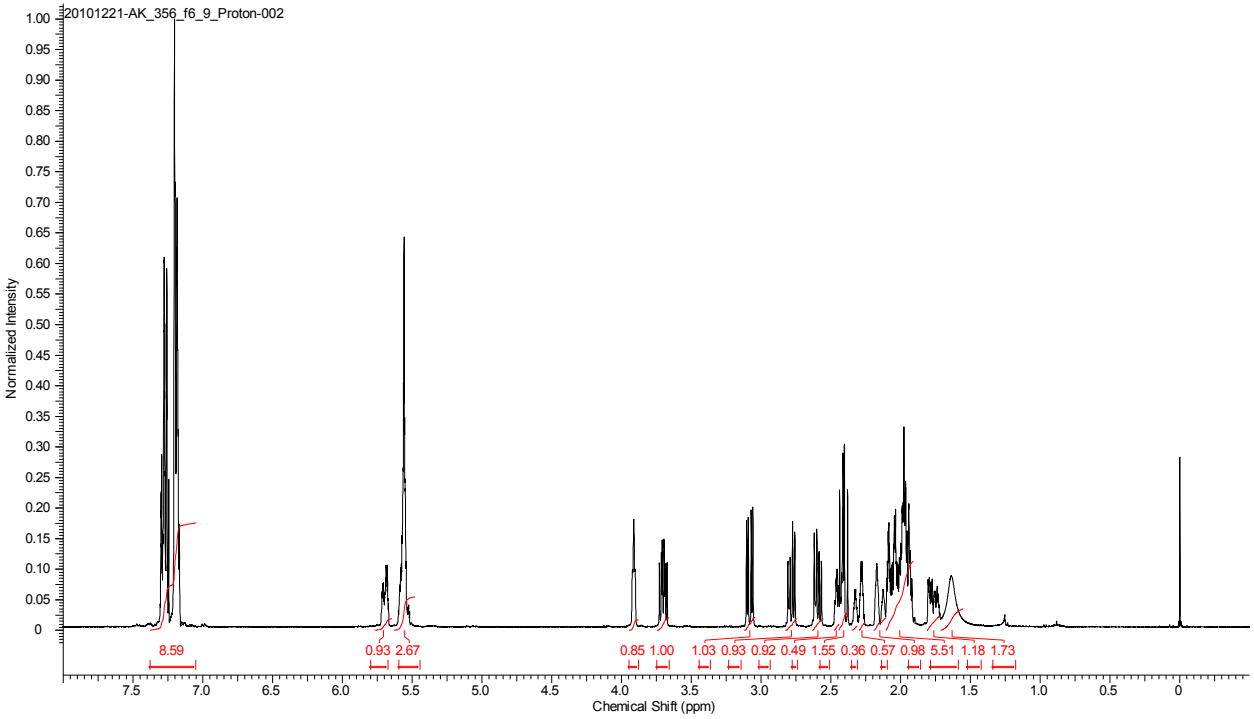

20101221-AK_357_f9_14_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

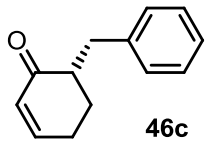

20101221-AK_357_f9_14_Proton-002
Normalized Intensity
1.00
4.73
0.92
1.11
3.10
1.09
Chemical Shift (ppm)


HO

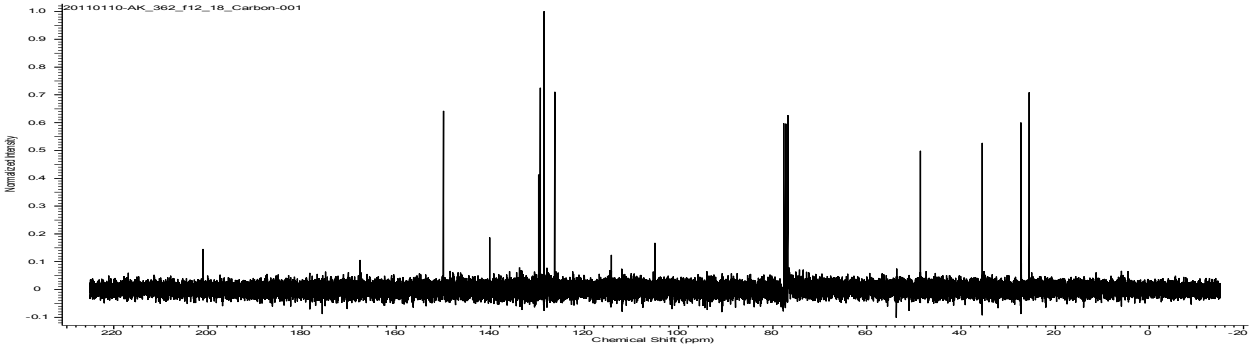
44c

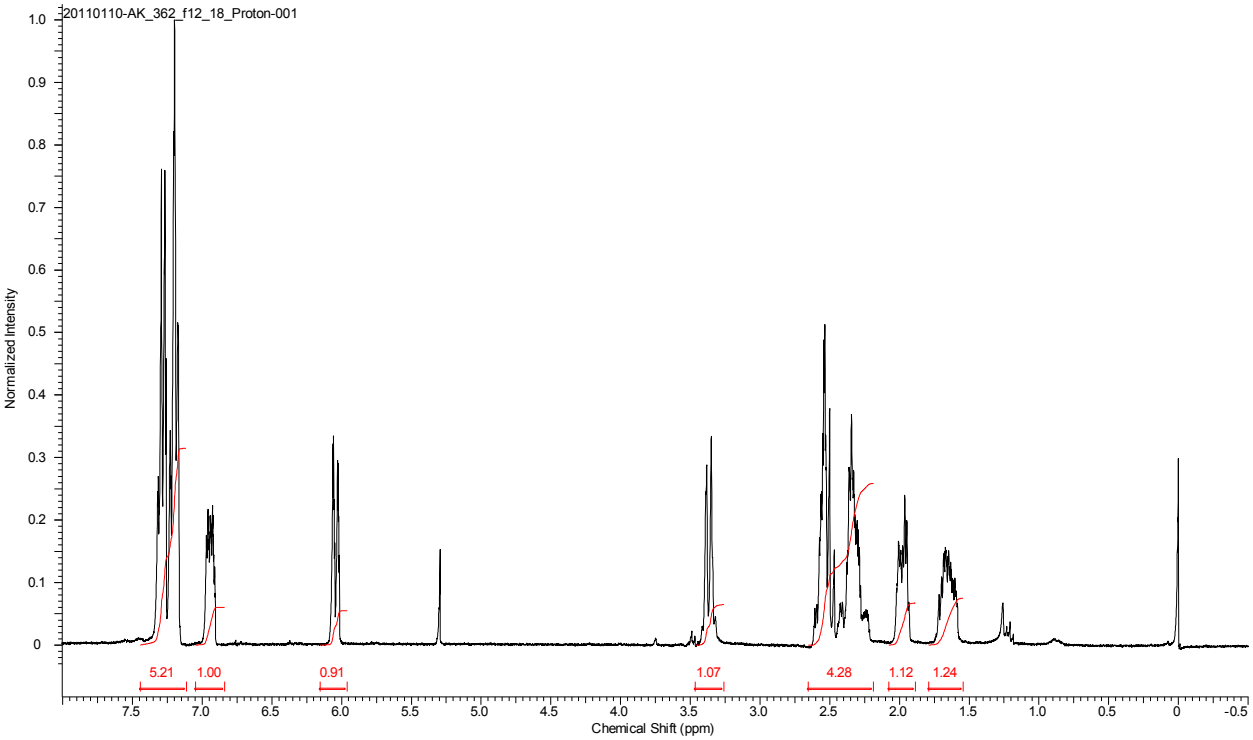

20101221-AK_356_f6_9_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

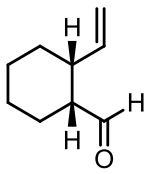

20101221-AK_356_f6_9_Proton-002
Normalized Intensity
8.59
0.93 2.67
0.85 1.00
1.03 0.93 0.92 0.49 1.55 0.36 0.57 0.98 5.51 1.18 1.73
Chemical Shift (ppm)



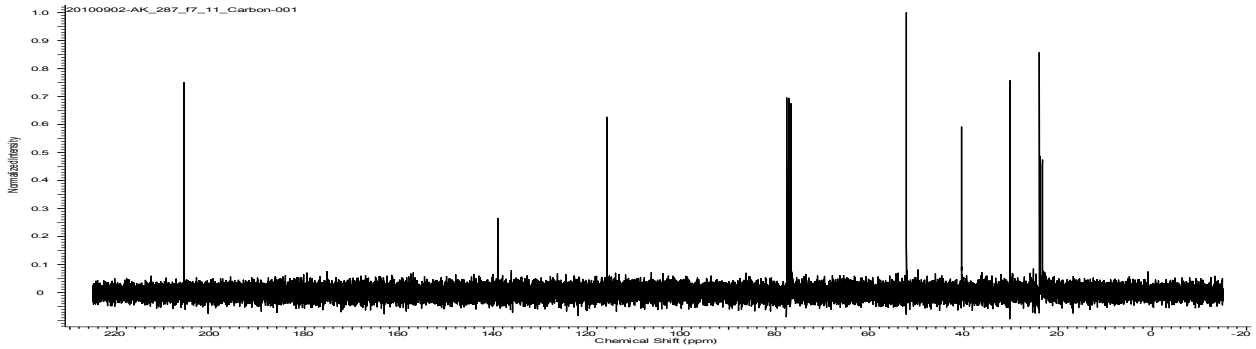
46c

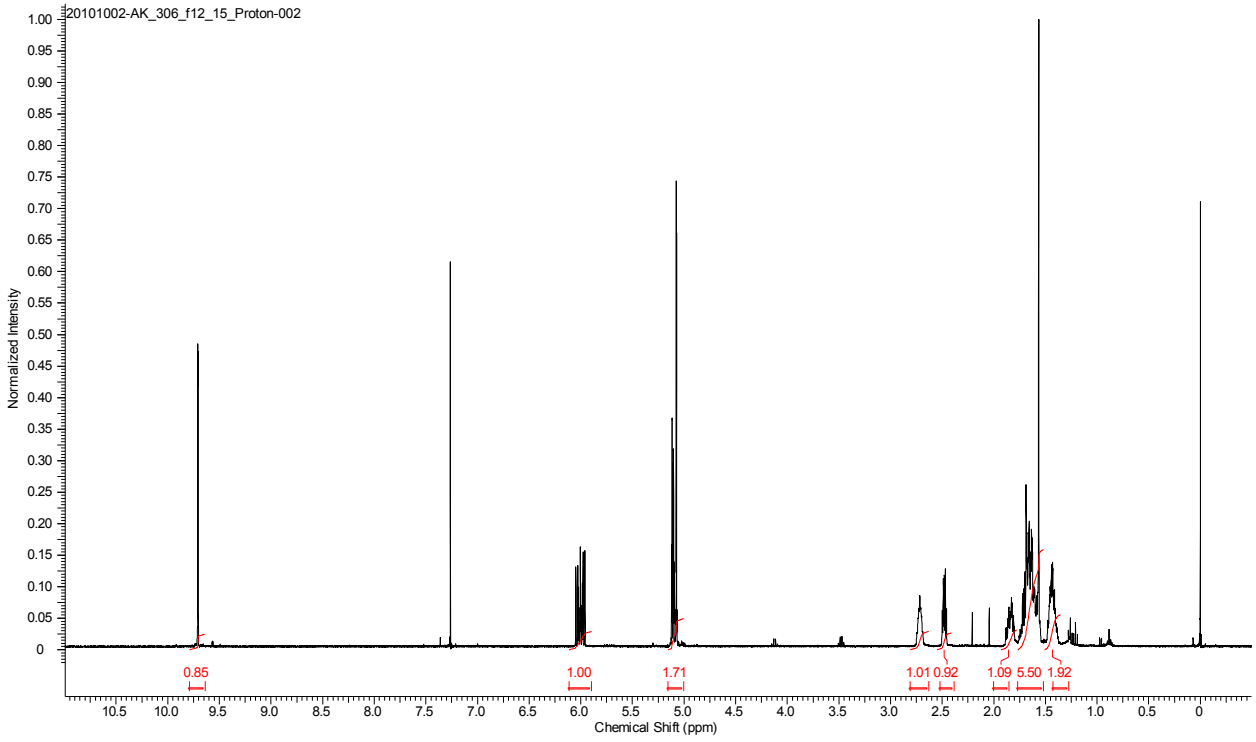

20110110-AK_362_f12_18_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

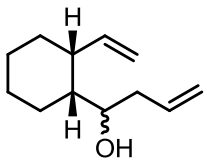

20110110-AK_362_f12_18_Proton-001
Normalized Intensity
5.21
1.00
0.91
1.07
4.28
1.12
1.24
Chemical Shift (ppm)


H
H
H
O

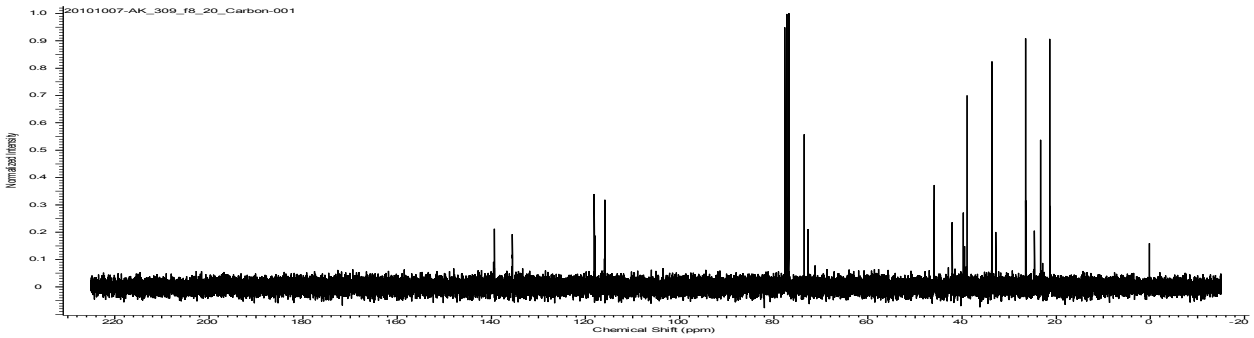
41d

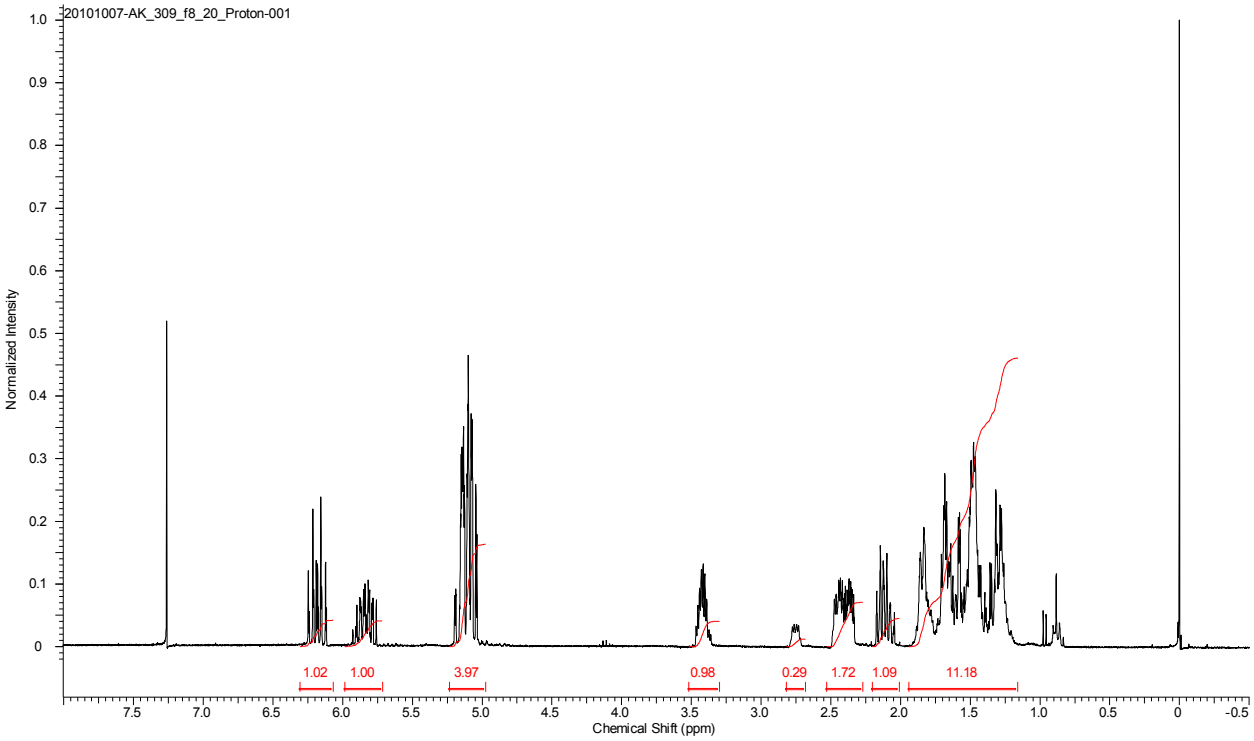

20100902-AK_287_f7_11_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

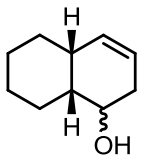

20101002-AK_306_f12_15_Proton-002
Normalized Intensity
0.85
1.00
1.71
1.01
0.92
1.09
5.50
1.92
Chemical Shift (ppm)


H
H
OH

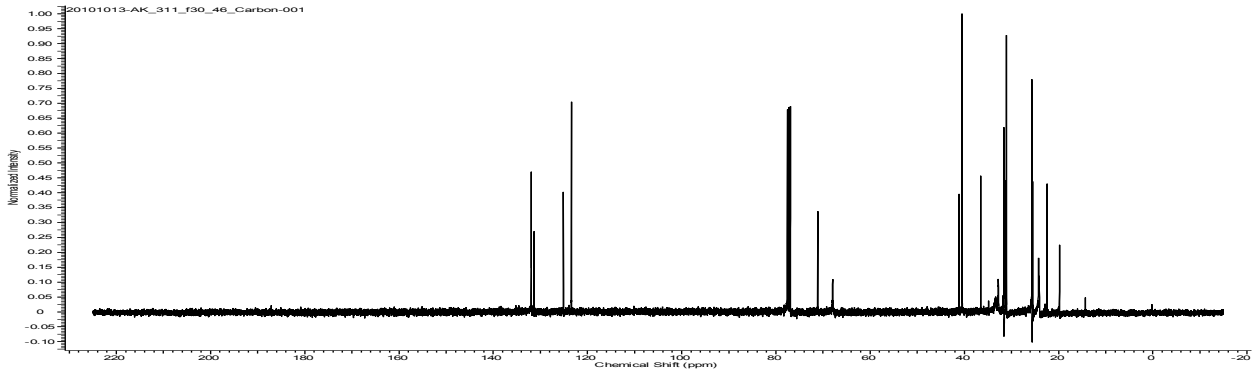
42d

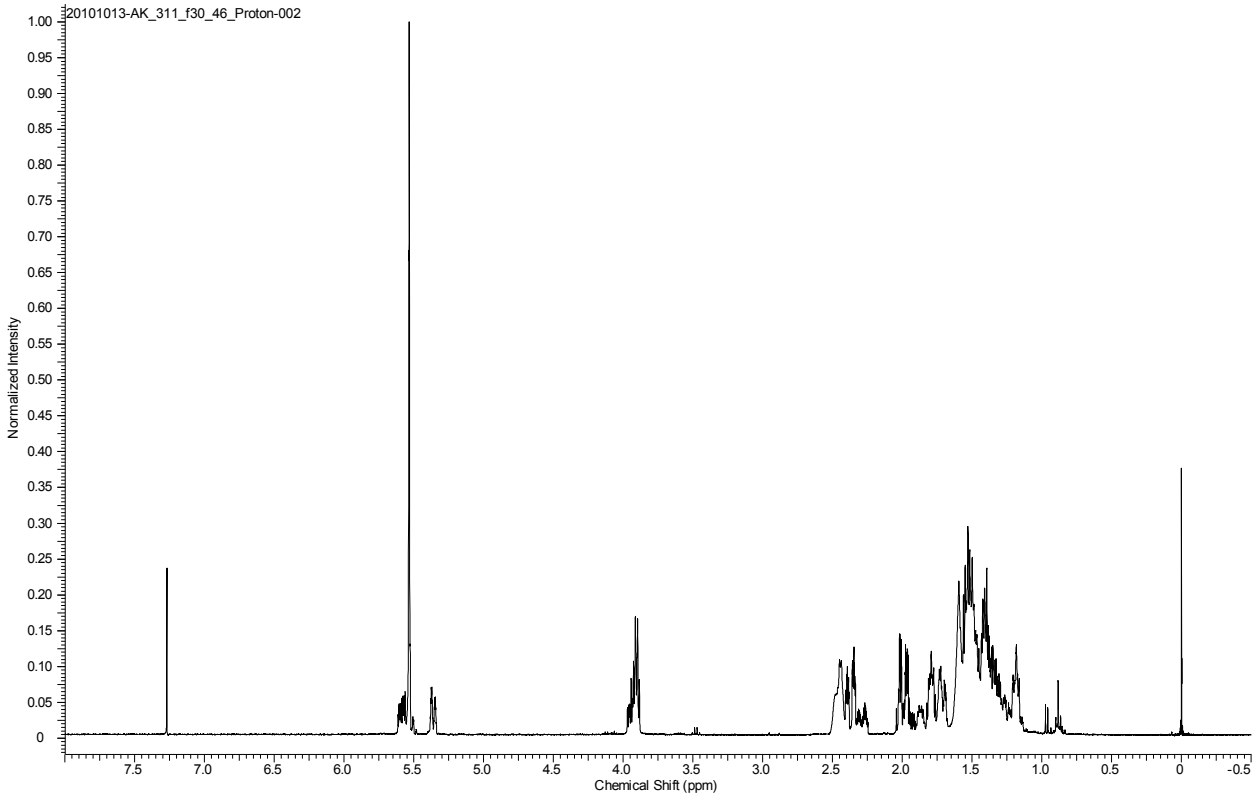

20101007-AK_309_f8_20_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

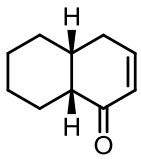

20101007-AK_309_f8_20_Proton-001
Normalized Intensity
1.02
1.00
3.97
0.98
0.29
1.72
1.09
11.18
Chemical Shift (ppm)


H
H
OH

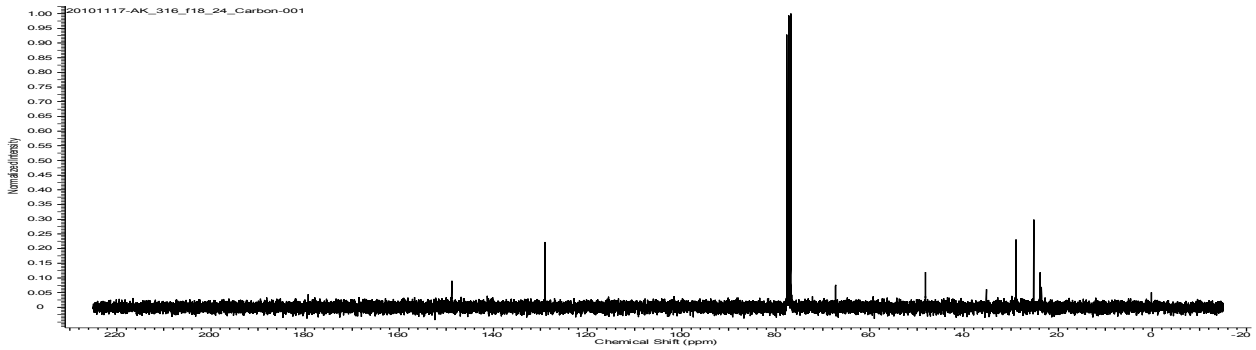
44d

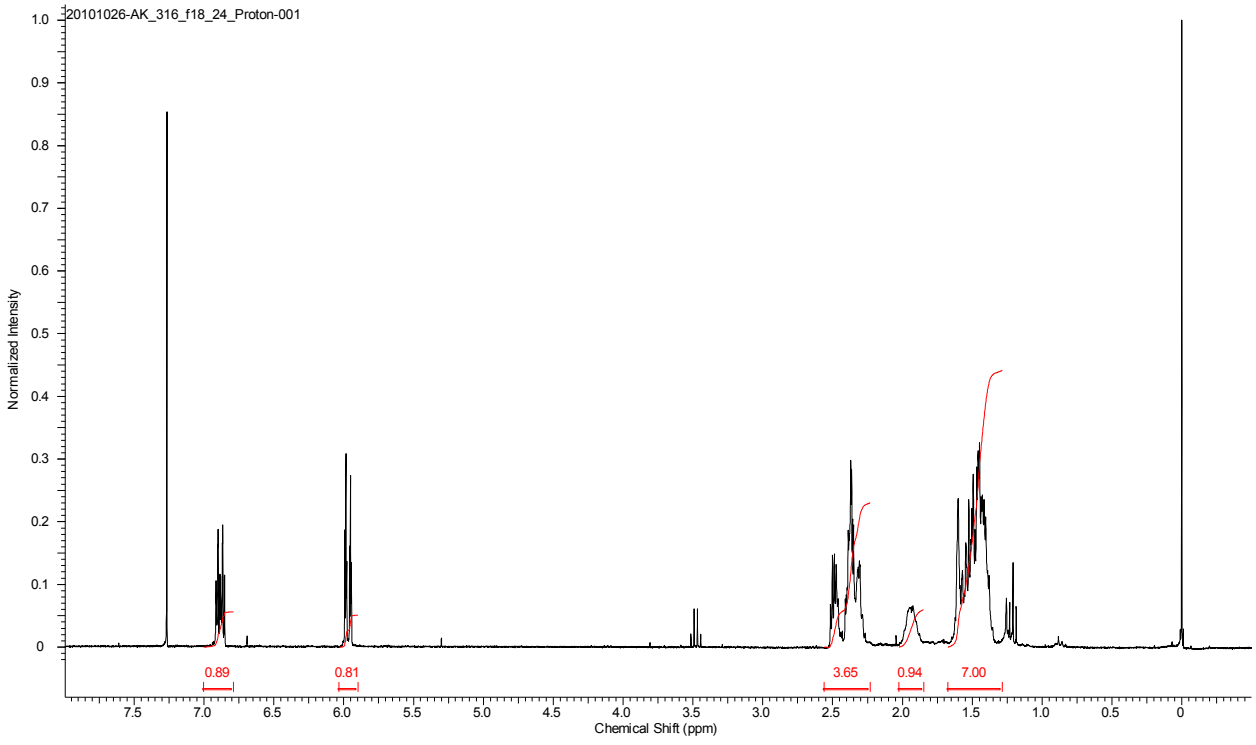

20101013-AK_311_f30_46_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

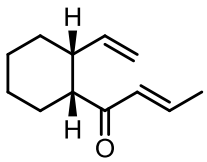

20101013-AK_311_f30_46_Proton-002
Normalized Intensity
Chemical Shift (ppm)


H
H
O

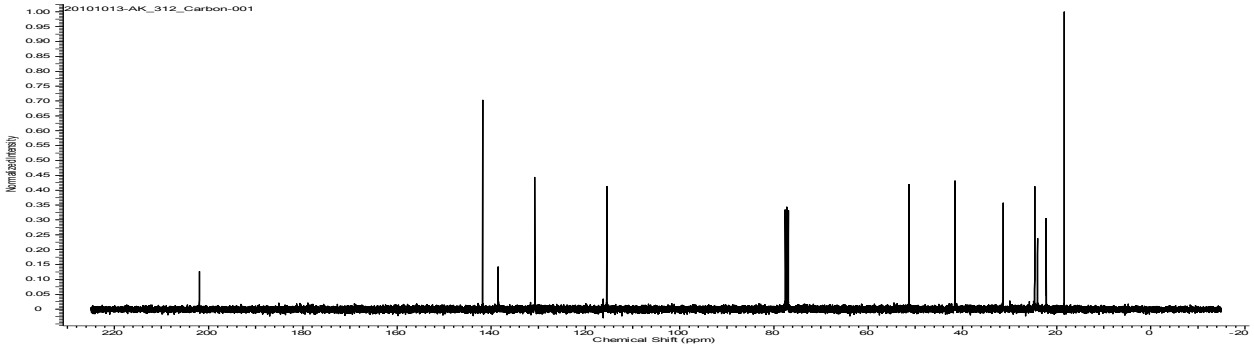
46d

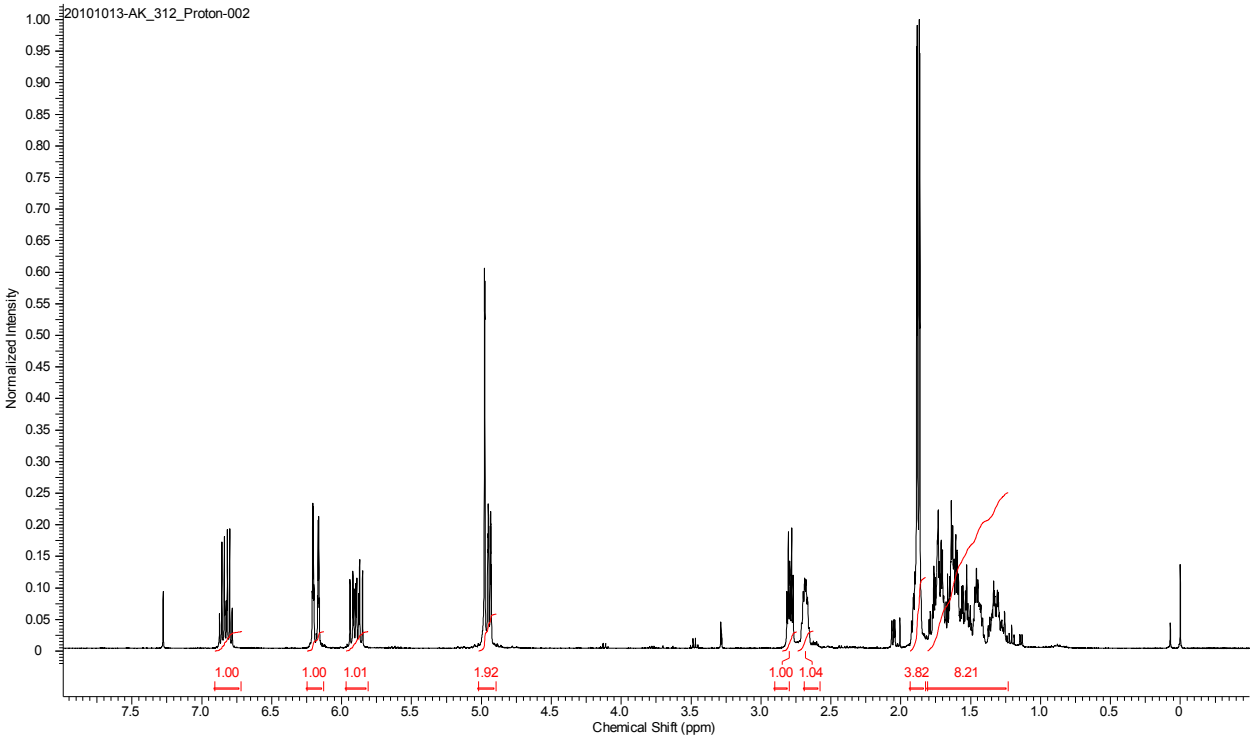

20101117-AK_316_f18_24_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

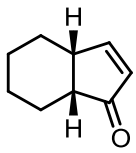

20101026-AK_316_f18_24_Proton-001
Normalized Intensity
0.89
0.81
3.65
0.94
7.00
Chemical Shift (ppm)


H
H
O

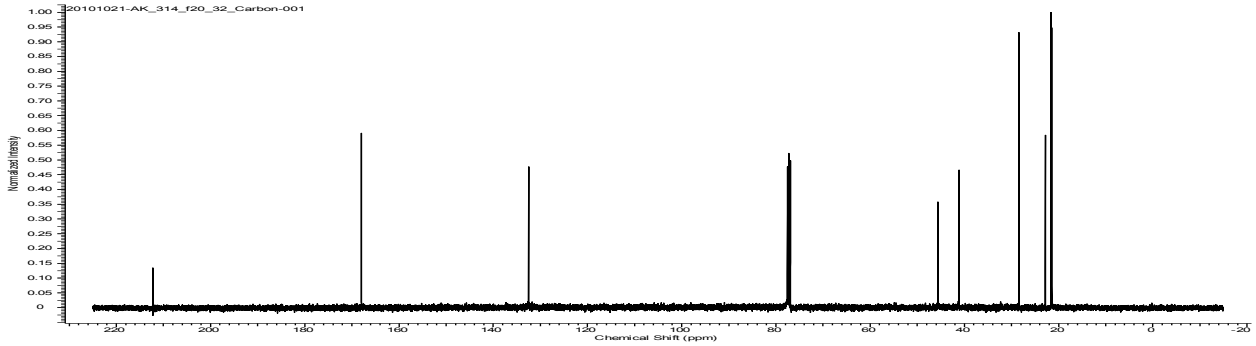
43d

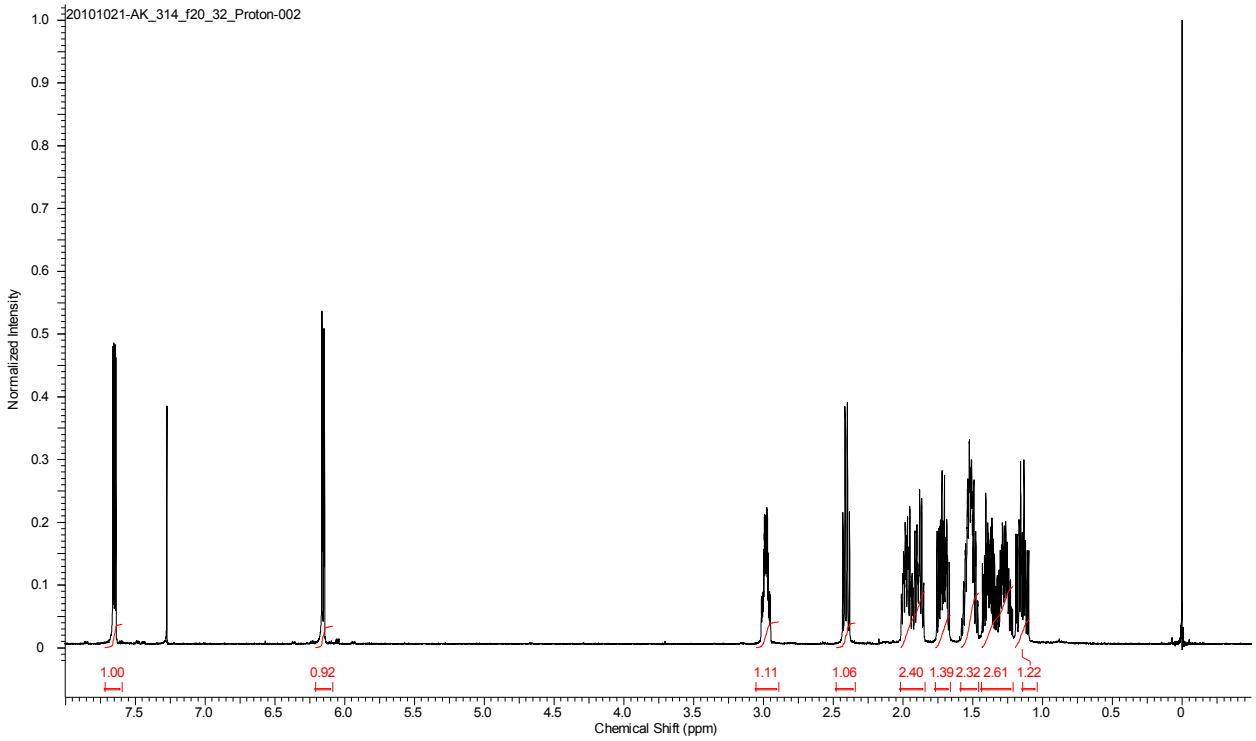

20101013-AK_312_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

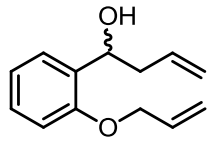

20101013-AK_312_Proton-002
Normalized Intensity
1.00
1.00
1.01
1.92
1.00
1.04
3.82
8.21
Chemical Shift (ppm)


H
H
O

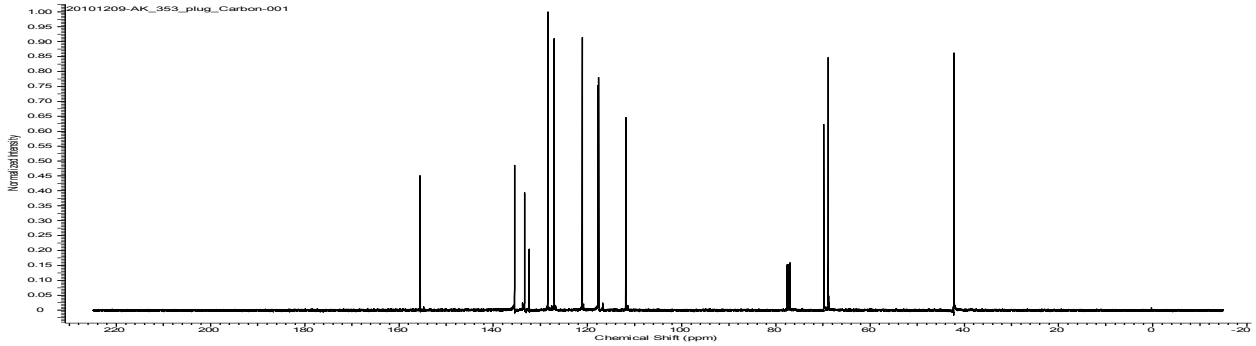
45d

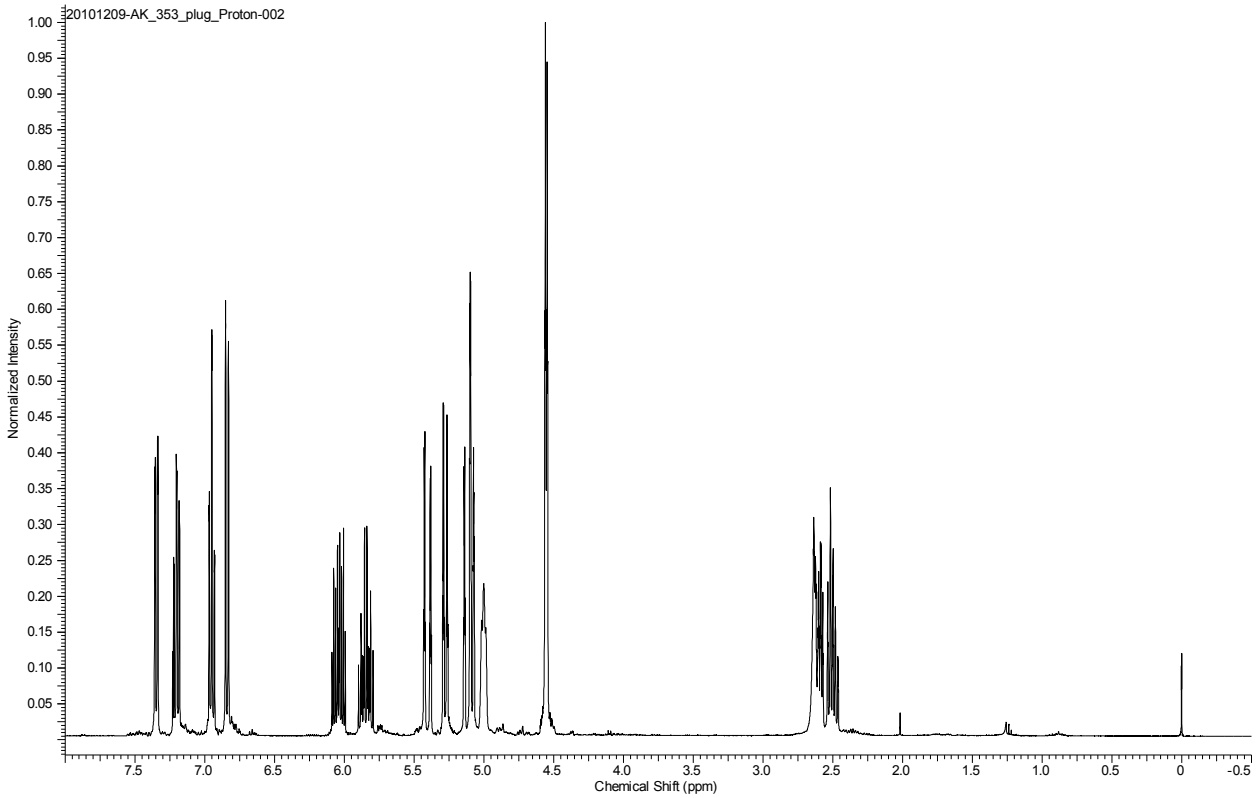

20101021-AK_314_f20_32_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

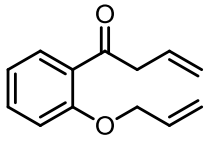

20101021-AK_314_f20_32_Proton-002
Normalized Intensity
1.00
0.92
1.11
1.06
2.40
1.39
2.32
2.61
1.22
Chemical Shift (ppm)


OH
O

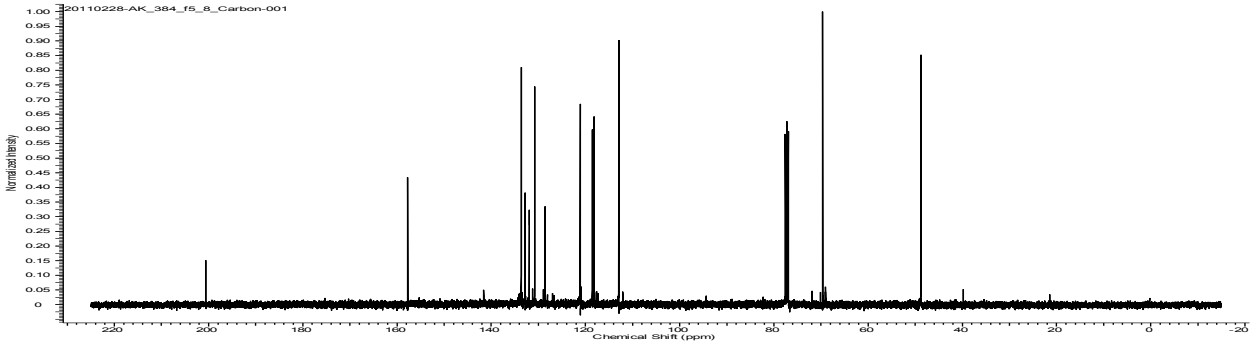
42e

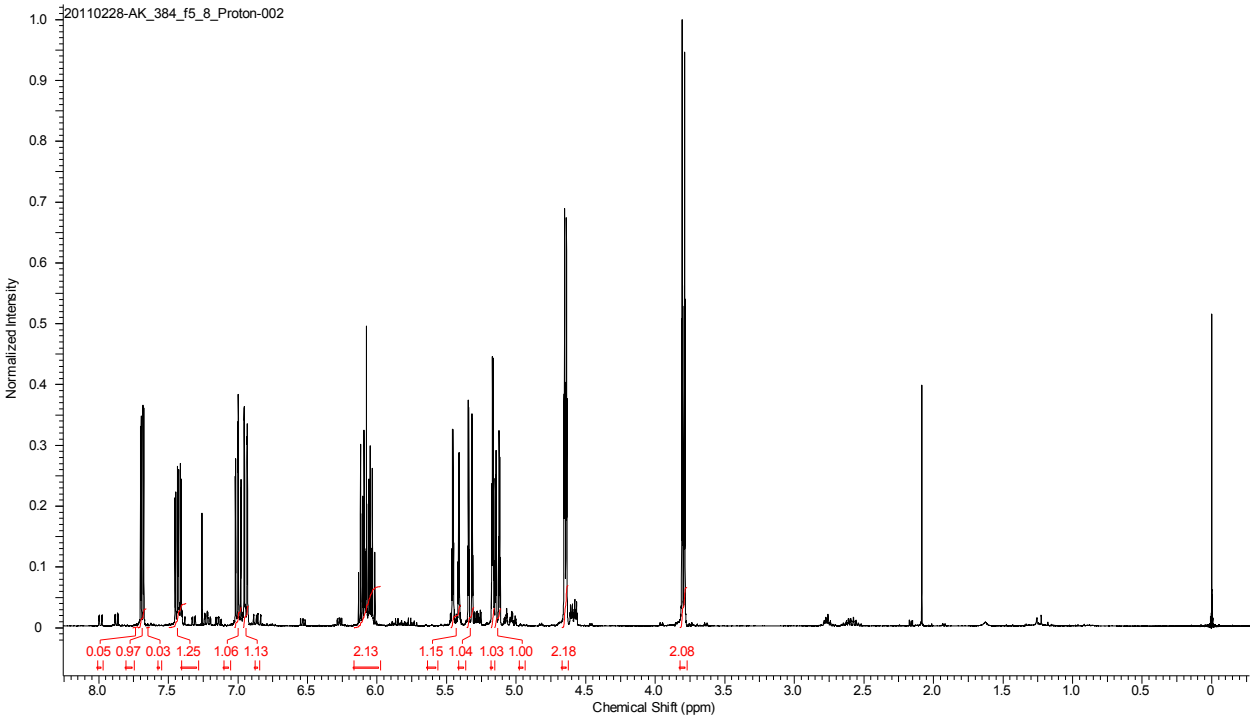

20101209-AK_353_plug_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

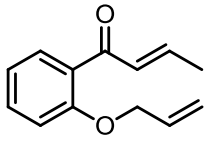

20101209-AK_353_plug_Proton-002
Normalized Intensity
Chemical Shift (ppm)



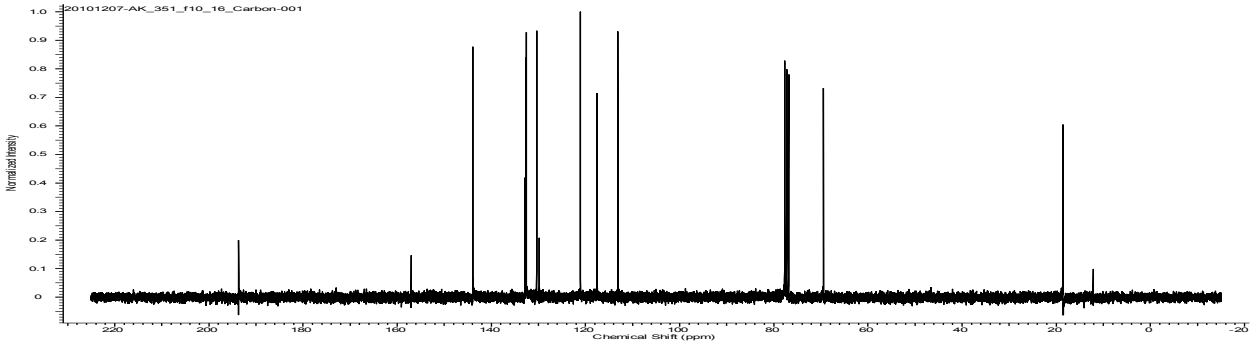
64

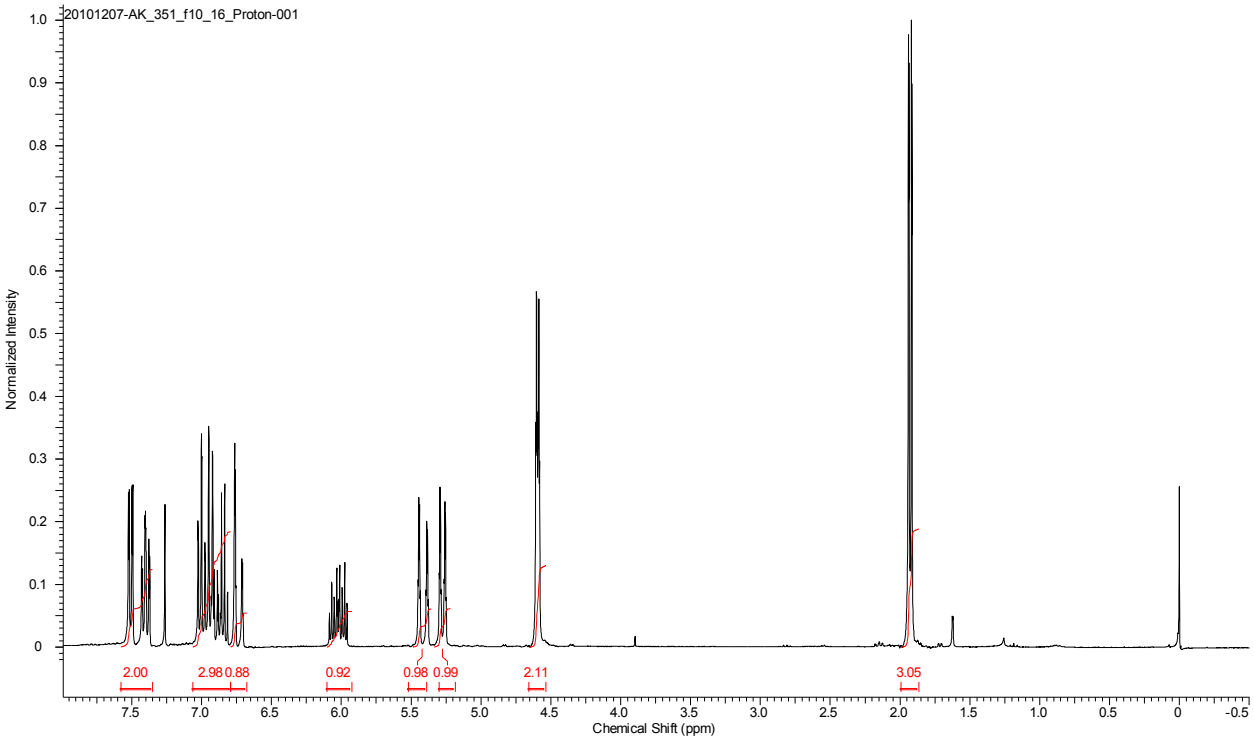

20110228-AK_384_f5_8_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

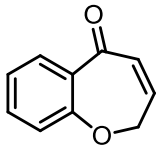

20110228-AK_384_f5_8_Proton-002
Normalized Intensity
0.05 0.97 0.03 1.25 1.06 1.13 2.13 1.15 1.04 1.03 1.00 2.18 2.08
Chemical Shift (ppm)



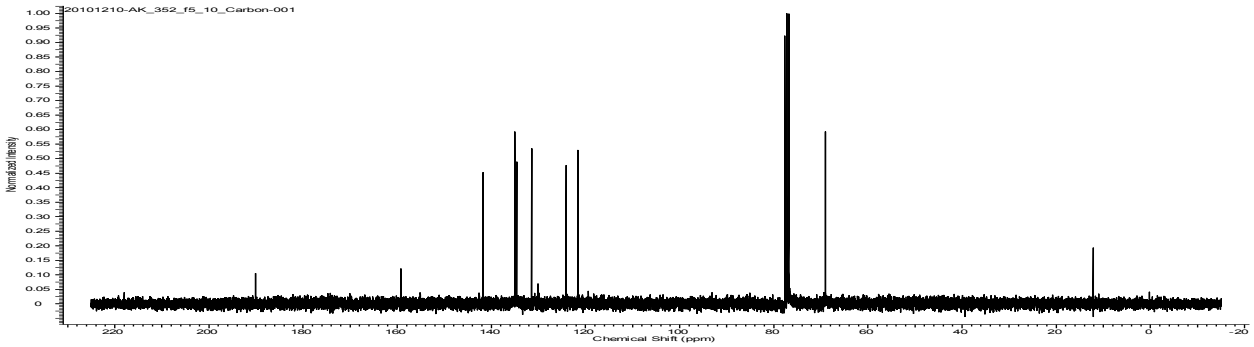
43e

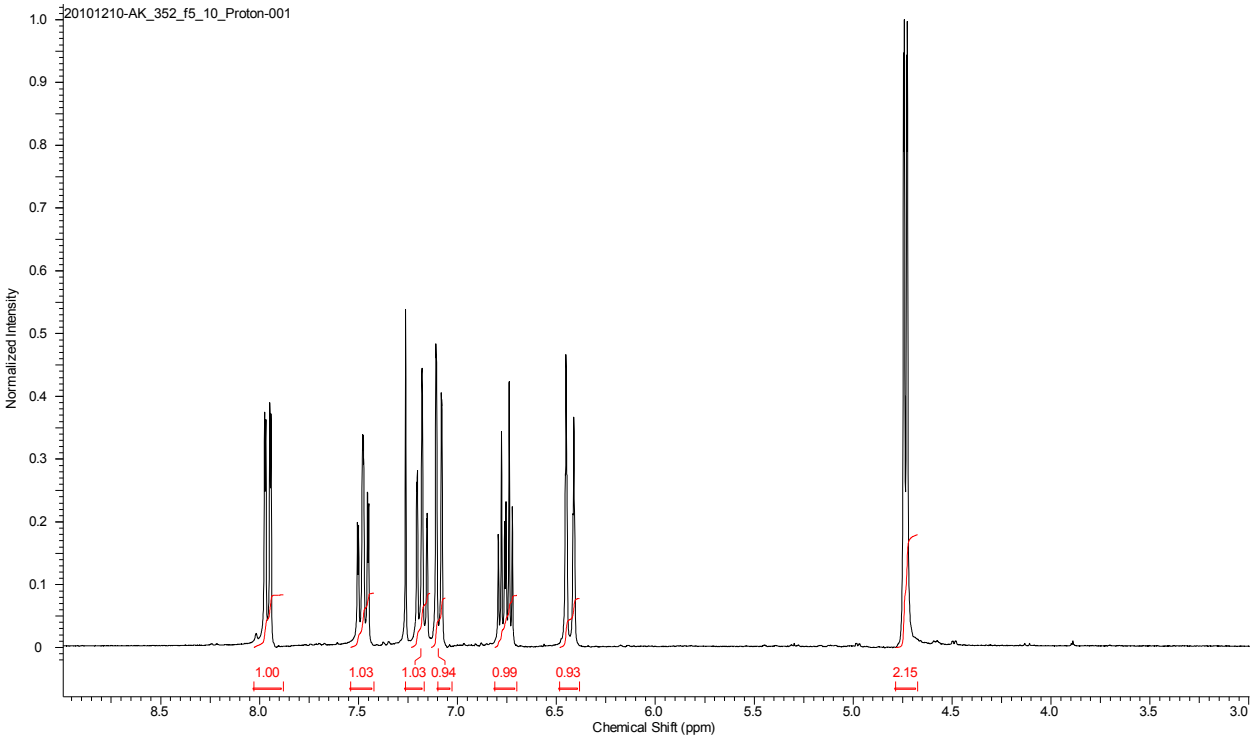

20101207-AK_351_f10_16_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

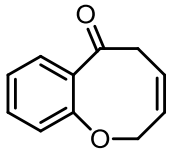

20101207-AK_351_f10_16_Proton-001
Normalized Intensity
2.00
2.98
0.88
0.92
0.98
0.99
2.11
3.05
Chemical Shift (ppm)



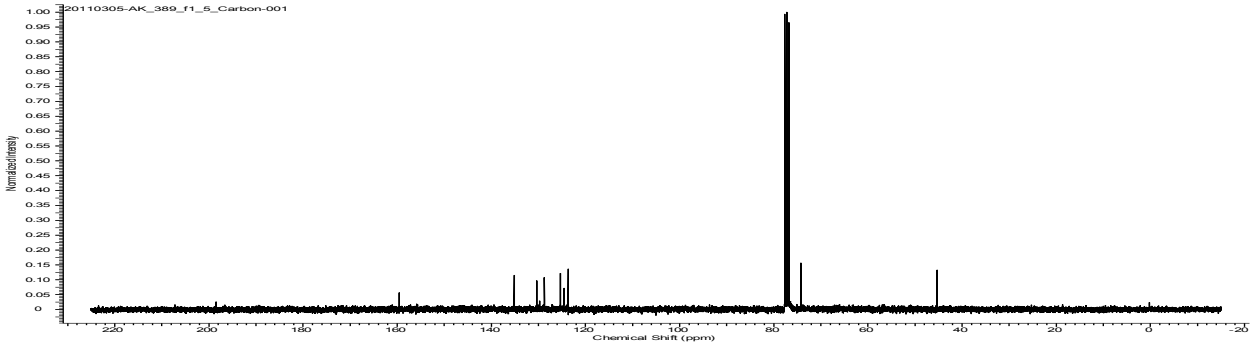
45e

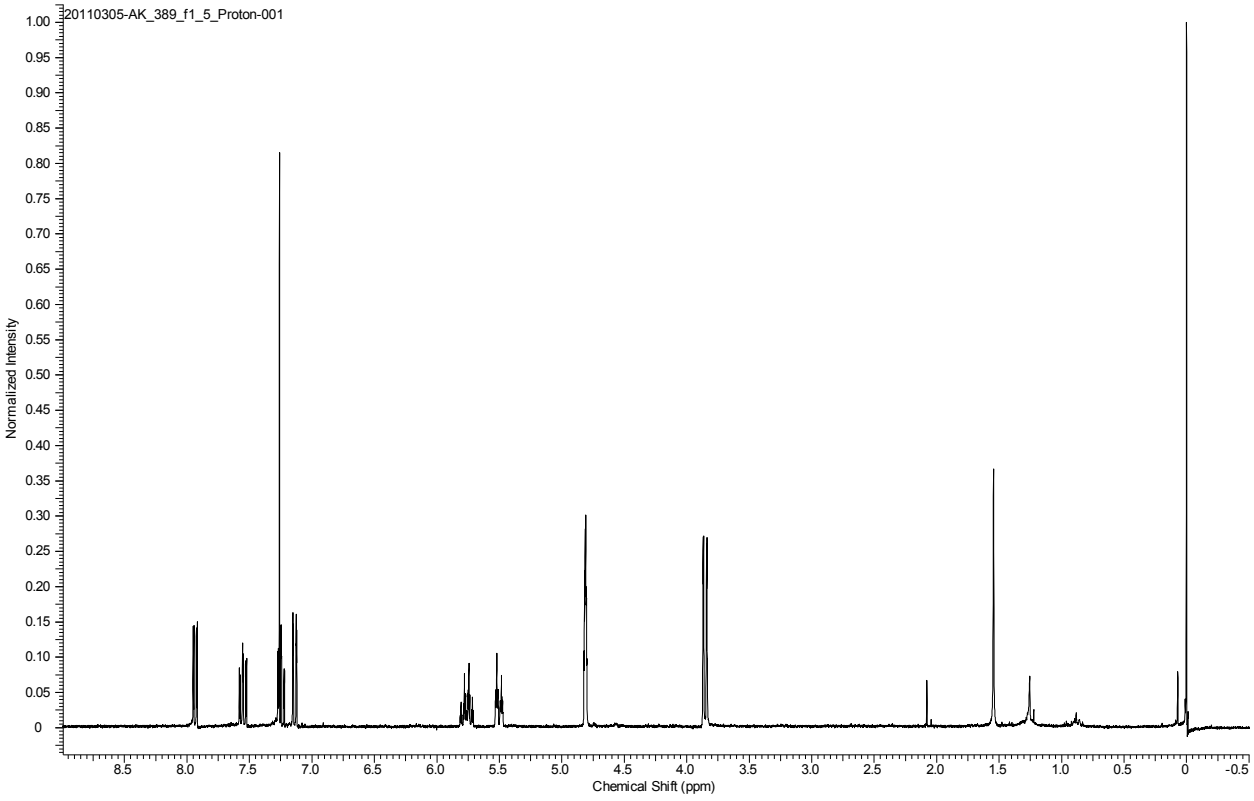

20101210-AK_352_f5_10_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

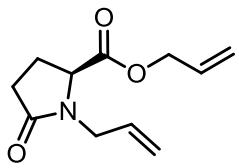

20101210-AK_352_f5_10_Proton-001
Normalized Intensity
1.00
1.03
1.03
0.94
0.99
0.93
2.15
Chemical Shift (ppm)



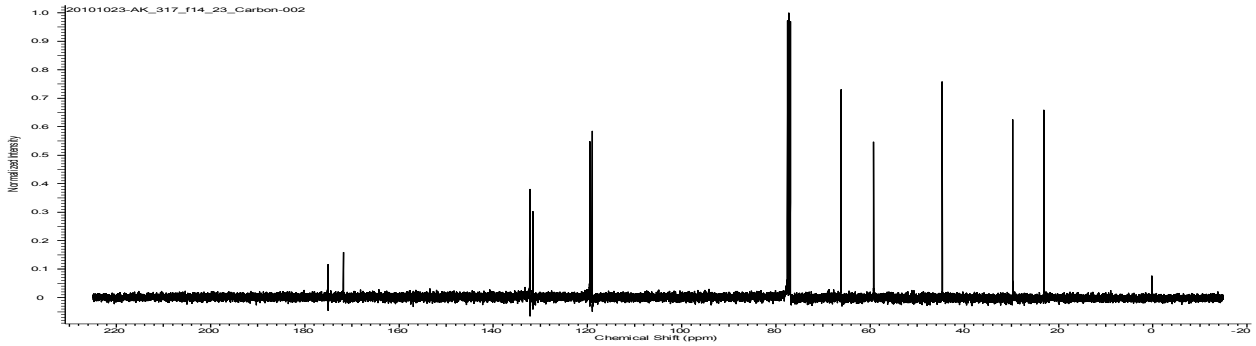
65

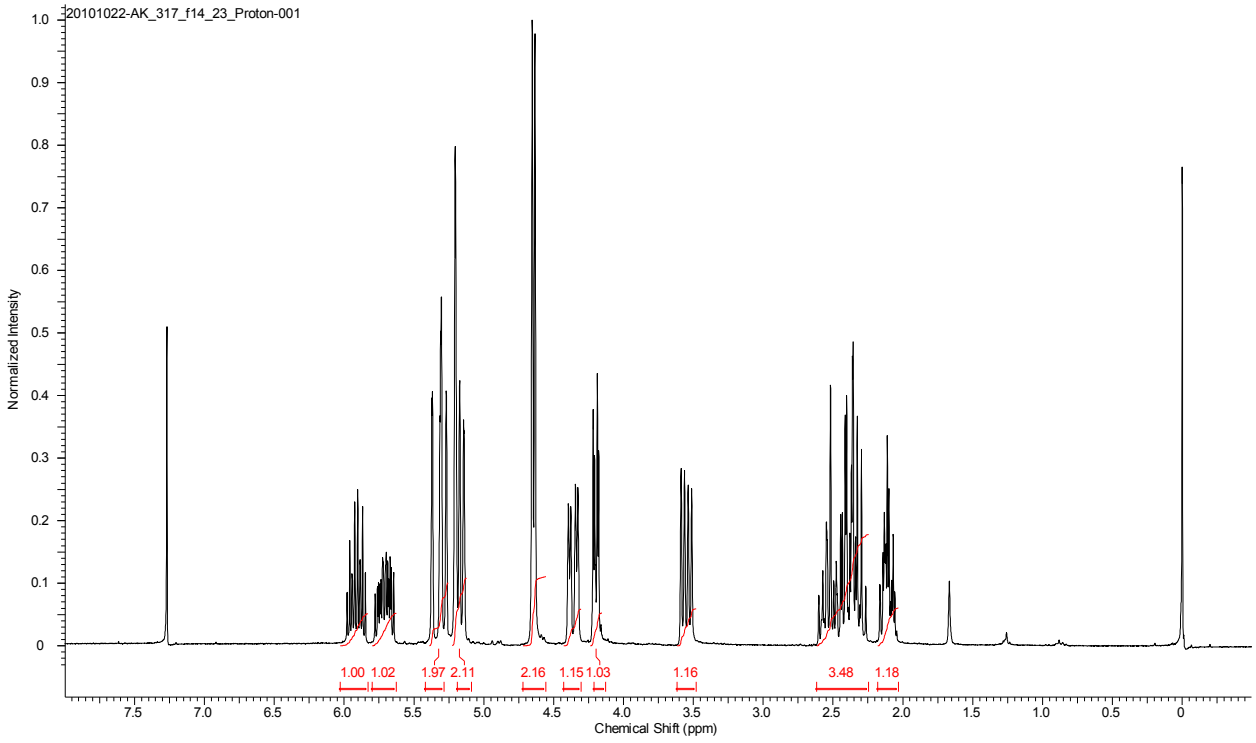

20110305-AK_389_f1_5_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

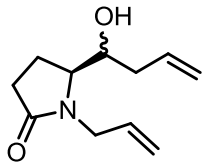

20110305-AK_389_f1_5_Proton-001
Normalized Intensity
Chemical Shift (ppm)



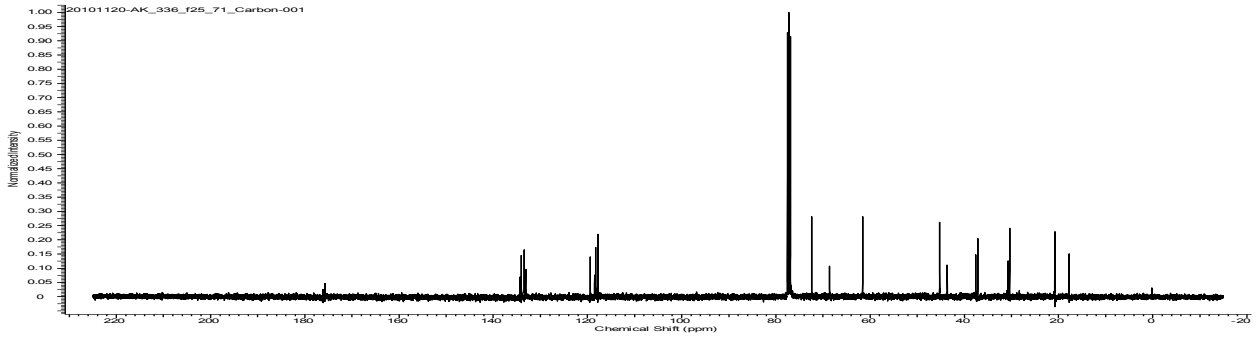
63

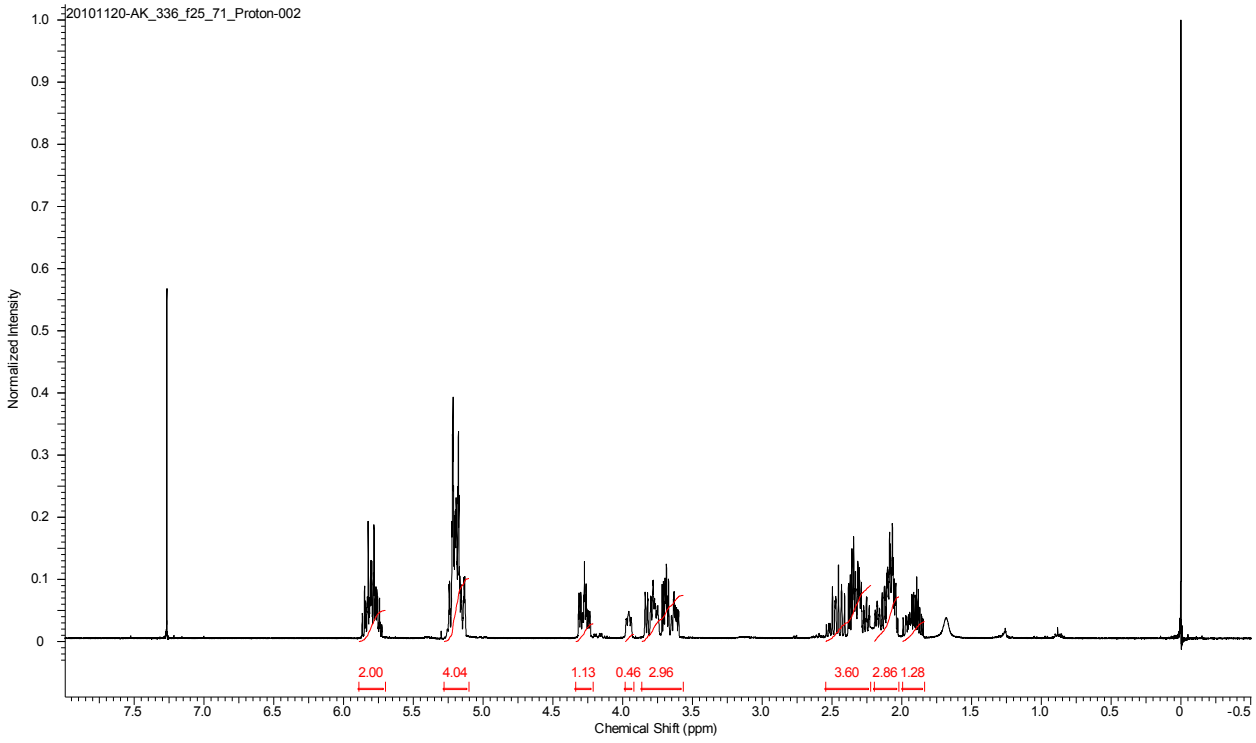

20101023-AK_317_f14_23_Carbon-002
Normalized Intensity
Chemical Shift (ppm)

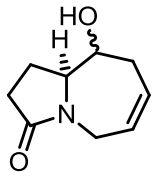

20101022-AK_317_f14_23_Proton-001
Normalized Intensity
1.00 1.02 1.97 2.11 2.16 1.15 1.03 1.16 3.48 1.18
Chemical Shift (ppm)


OH
N
O

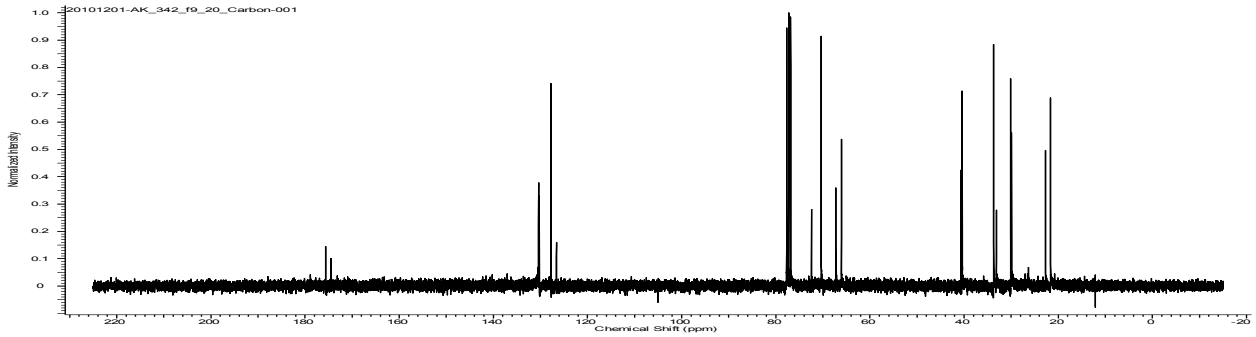
42f

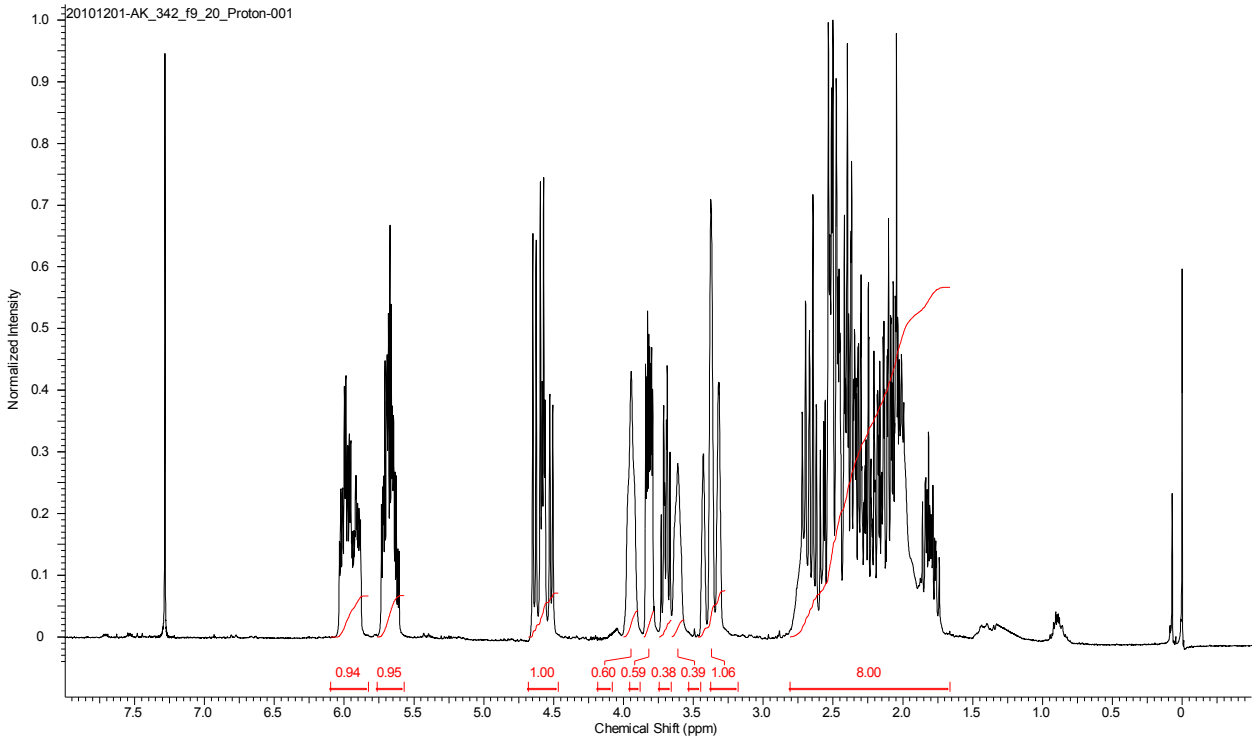

20101120-AK_336_f25_71_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

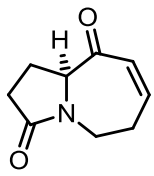

20101120-AK_336_f25_71_Proton-002
Normalized Intensity
2.00
4.04
1.13
0.46
2.96
3.60
2.86
1.28
Chemical Shift (ppm)


HO
H
N
O

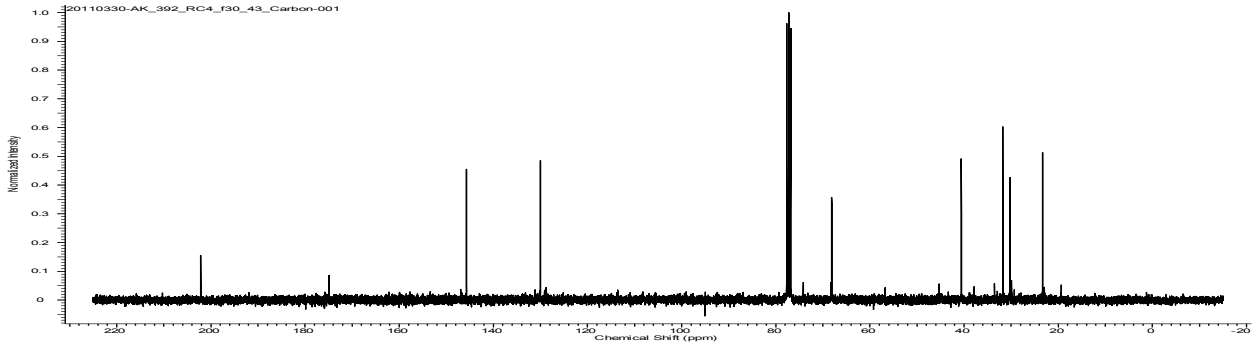
44f

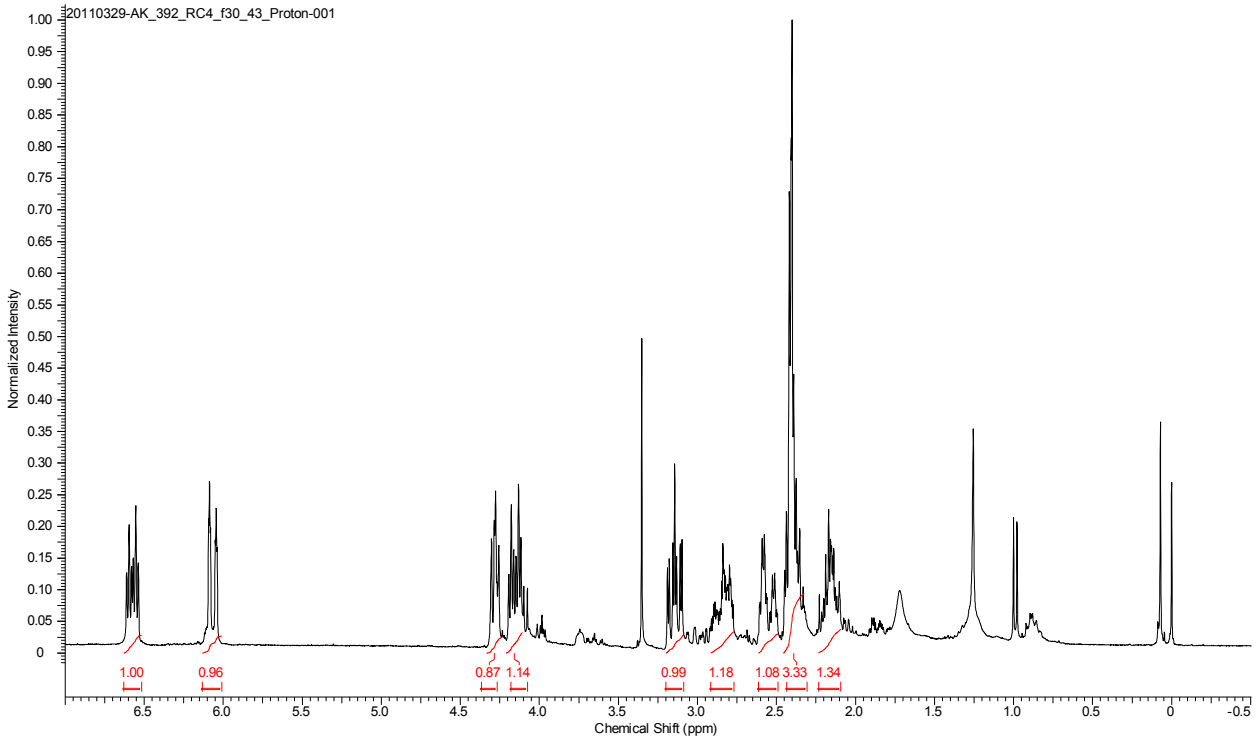

20101201-AK_342_f9_20_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

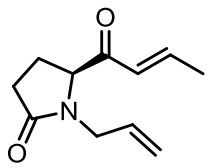

20101201-AK_342_f9_20_Proton-001
Normalized Intensity
0.94
0.95
1.00
0.60
0.59
0.38
0.39
1.06
8.00
Chemical Shift (ppm)



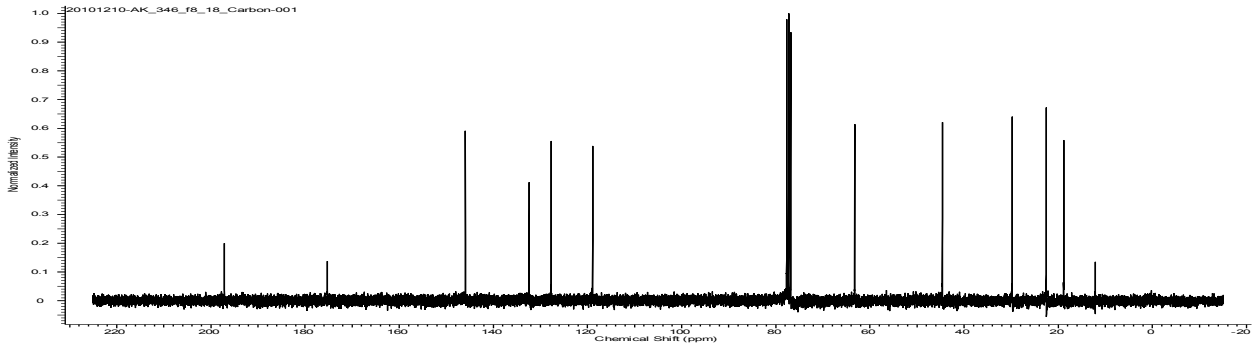
46f

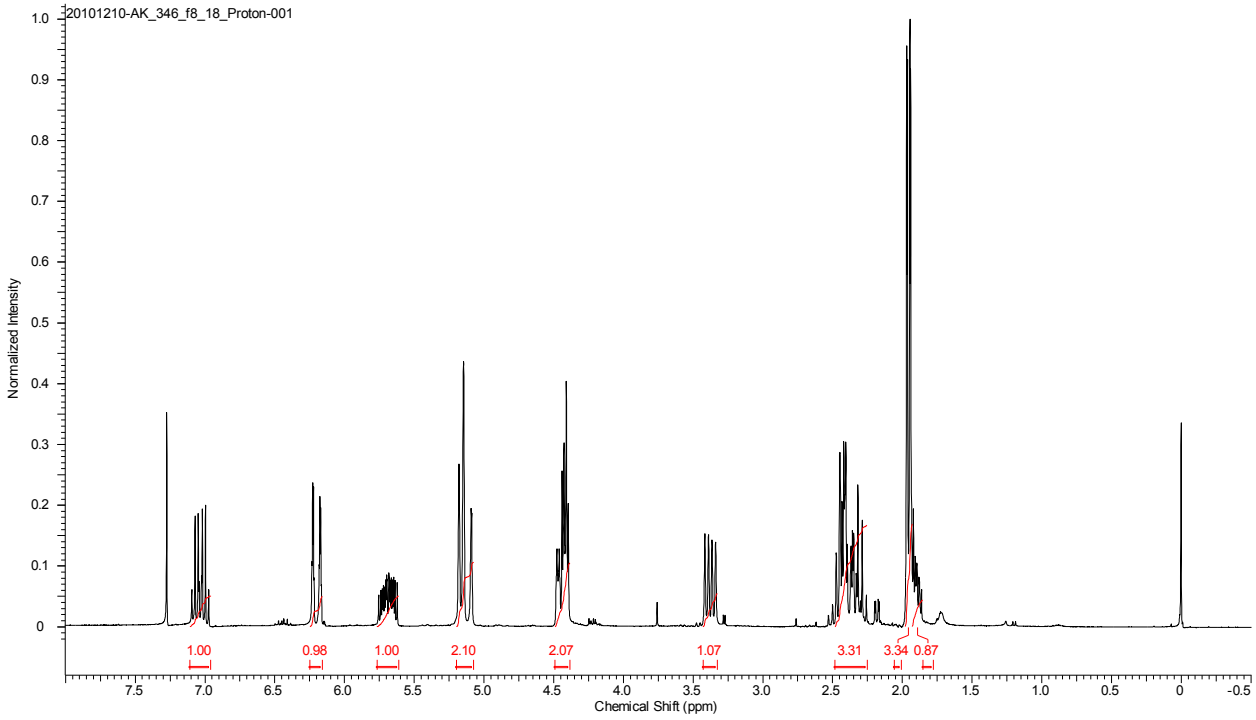

20110330-AK_392_RC4_f30_43_Carbon-001
Normalized Intensity
Chemical Shift (ppm)

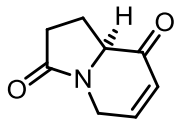

20110329-AK_392_RC4_f30_43_Proton-001
Normalized Intensity
1.00
0.96
0.87
1.14
0.99
1.18
1.08
3.33
1.34
Chemical Shift (ppm)



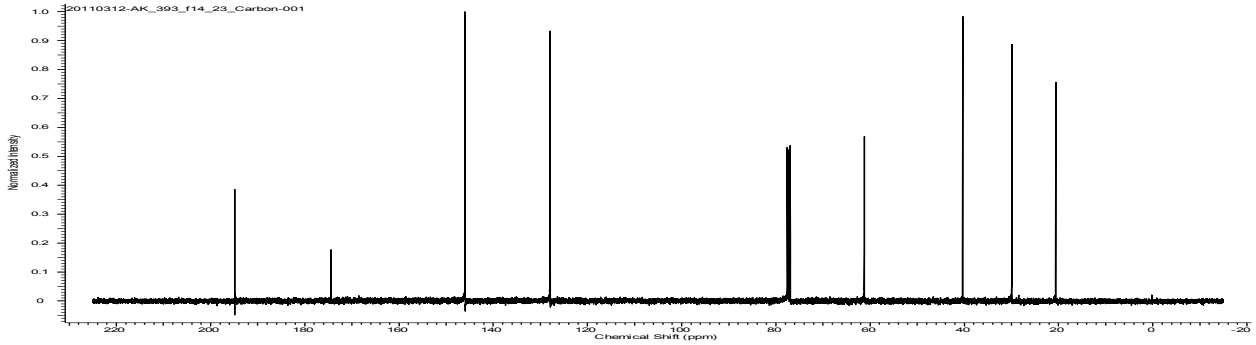
43f

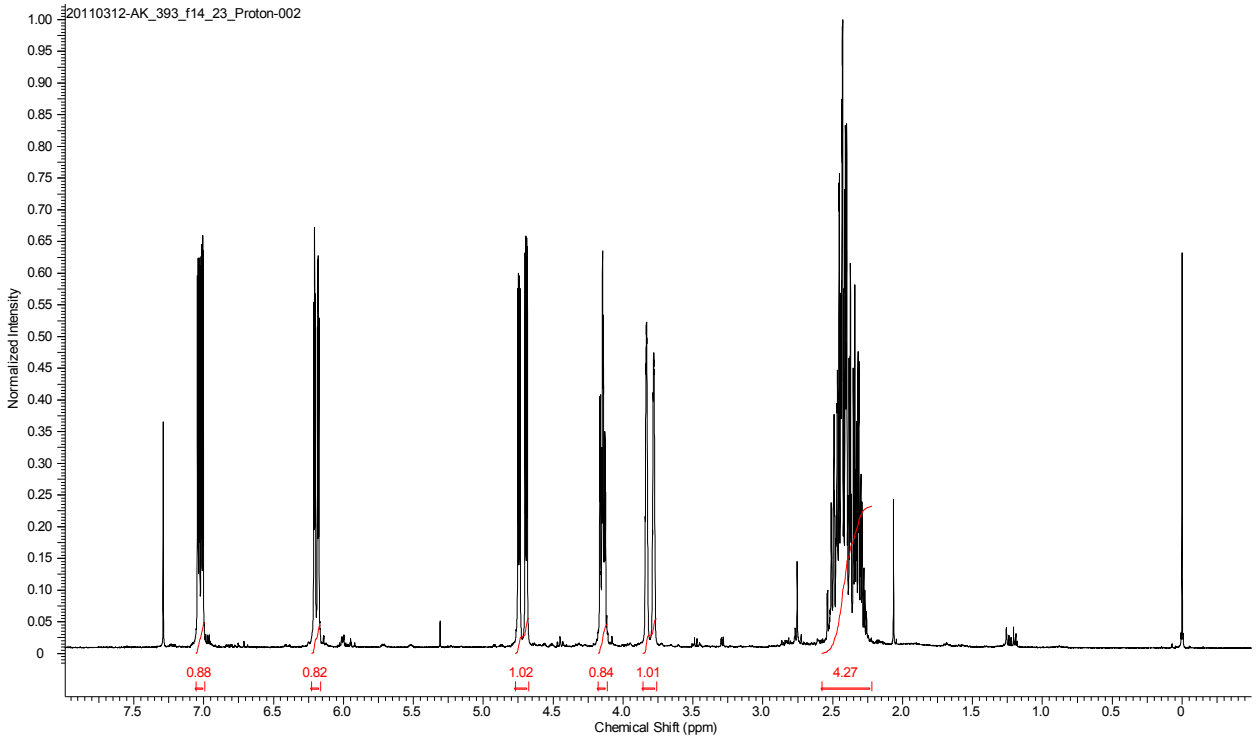

20101210-AK_346_f8_18_Carbon-001
Normalized Intensity
Chemical Shift (ppm)


20101210-AK_346_f8_18_Proton-001
Normalized Intensity
1.00
0.98
1.00
2.10
2.07
1.07
3.31
3.34
0.87
Chemical Shift (ppm)


H
O
O
N

45f


20110312-AK_393_f14_23_Carbon-001
Normalized Intensity
Chemical Shift (ppm)


20110312-AK_393_f14_23_Proton-002
Normalized Intensity
0.88
0.82
1.02
0.84
1.01
4.27
Chemical Shift (ppm)

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