I. A TANDEM DEALKOXYCARBONYLATION MICHAEL ADDITION ROUTE TO HIGHLY FUNCTIONALIZED CYCLOHEXANE-ACETIC ESTERS

II. A TANDEM DEALKOXYCARBONYLATION-MICHAEL ADDITION ROUTE TO FIVE- AND SIX-MEMBERED LACTAMS AND LACTONES

III. THE SYNTHESIS OF ^{13}C-LABELED δ-AMINOLEVULINIC ACIDS

By

CURTIS L. SCHILLING III

Bachelor of Science

State University of New York, College at Oswego

Oswego, New York 1989

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
December, 1996

I. A TANDEM DEALKOXYCARBONYLATION MICHAEL ADDITION ROUTE TO HIGHLY FUNCTIONALIZED CYCLOHEXANE-ACETIC ESTERS

II. A TANDEM DEALKOXYCARBONYLATION-MICHAEL ADDITION ROUTE TO FIVE- AND SIX-MEMBERED LACTAMS AND LACTONES

III. THE SYNTHESIS OF ^{13}C-LABELED δ-AMINOLEVULINIC ACIDS

Thesis Approved:

Richard A. Bunce
Thesis Advisor

Warren T Ford

Horacio A Mottola

Elizabeth M Holt

Richard C Bassleer

Thomas C. Collins
Dean of the Graduate College

ACKNOWLEDGEMENTS

I would like to offer my sincere gratitude to my research adviser, Dr. Richard A. Bunce for giving me the opportunity to benefit from his tutelage. He is a veritable fountain of knowledge concerning organic chemistry and research technique and I will be hard-pressed to aspire to that level of competence. My tenure at OSU has had many ups and downs, but Dr. Bunce was a constant presence throughout. In a time when many issues are settled with weapons, we never failed to resolve things with a good sense of humor. I would also like to thank my graduate committee; Dr. Richard Essenberg, Dr. Warren T. Ford, Dr. Elizabeth M. Holt, and Dr. Horatio A. Mottola, several of whom I have had the pleasure of taking classes from. I have gleaned valuable knowledge, not always about chemistry, from all of you. Dr. Mario Rivera and Dr. Steven Graham have also provided input at key points that contributed to my success. In addition, the support staff for the department, Stan Sigle, Tom Denton, Herold Brown, Cindy Price, June Williams, and Carolyn Schwabe have all, at one time or another, helped me out. My compatriots in the lab made comfortable an otherwise potentially psychosis-producing environment. Many of Dr. Bunce's former and current students made the list; Paul Jones, Eric Dowdy, Shawn Childress, Scrappy (for amusement purposes only), Charles "Albert Schvitzer" Wells and Joel "Loose Cannon" Moore. I have made many friends in the department since my arrival and several stand out as above average in their helpfulness; Greg Garrison, Tim Smith, Paul West, Tracey Yates, Matora Madler, Robert Parkhill, and Dr. Gil Mains have all contributed to how I am today.

Finally, I would like to thank those organizations that provided financial support; the Graduate College, the Chemistry department, the Jonas Fellowship, Dr. Bunce, and Dr. Rivera.

I would like to take this opportunity to express in writing the deep debt I owe my wife Tracy. She has endured 4 years of graduate school without having to go to school. I'm not sure this is what she hoped for when we used our honeymoon trip to move out here instead of going to Europe. Her words of encouragement and understanding always managed to defuse a long day at the office. I owe you big time.

Finally, I would like to dedicate this thesis to my parents, Curtis and Betty Anne Schilling, who never gave up on me. Where other parents might have been content they knew I could achieve more and did everything in their power to see that I had that opportunity. They were always there with moral support and an open ear to my problems. It was a long journey and not one I'm sure I would undertake again. My father has always been a source of inspiration, showing that hard work will get you where you want to go if you have the patience. My mother is exemplary at proving that PhD's don't know everything and common sense is just as valuable as a sheepskin sometimes. Thank you both for all you have done. You both deserve as much credit for this degree as I do.

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Figure Page

Chapter 5

Figure Page

Chapter 6

Figure Page

LIST OF TABLES

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 1

Historical Background: Ring Expansion Reactions and Their Application to Organic Synthesis

Introduction

The ring expansion reaction is a powerful tool to access larger ring systems.[1] The literature is full of processes dedicated to enlarging ring systems by varying numbers of carbons. The sources of the additional carbons are many. This chapter will give a general background on the various types of ring expansion reactions with an emphasis on those reactions that classify as one-carbon insertions or side-chain incorporations.

One-Carbon Insertion Reactions

In considering the various types of ring expansion reactions, a specific reaction is usually classified by the source of the additional carbons added to the ring.[1] The general class of one-carbon ring insertions is one of the larger groups of ring expansion reactions. The inserted carbon can be incorporated either intra- or intermolecularly. The atom to be inserted is not limited to carbon; oxygen or nitrogen heterocycles can also be prepared by one-atom ring expansion. The number of reactions available to effect a one-carbon insertion is staggering and a complete listing is beyond the scope of this review. Luckily, the fundamental types of reactions are few and only selected examples of each will be considered in this segment.

The pinacol rearrangement represents a common theme among ring expansion processes.[2] Acid-catalyzed dehydration of 1,2-diols generates a carbocation. Donation of

the oxygen lone pair of the adjacent hydroxyl generates a protonated carbonyl, causing a 1,2-alkyl shift which enlarges the ring by one carbon. Formation of the carbonyl and relief of ring strain are the driving forces behind the rearrangement. Paquette and Wang[3] used the pinacol rearrangement as a key step in the enantioselective synthesis of (-)-grindelic acid **3** (Figure 1).

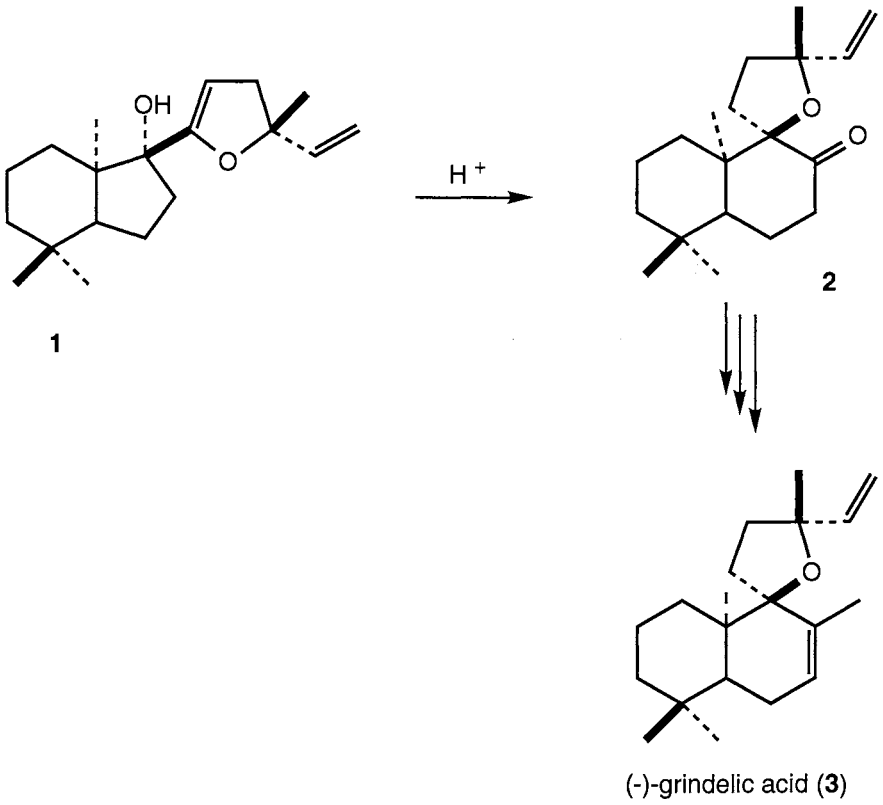


Figure 1. Synthesis of (-)-Grindelic Acid.

In another acid-catalyzed process similar to the pinacol rearrangement, the Wagner-Meerwein rearrangement occurs if β-alkyl substituted alcohols are treated with acid. Protonation and the subsequent loss of water sets up a 1,2-alkyl shift. The resulting carbocation reacts by either the loss of an α-hydrogen or addition of a nucleophile. Cho and co-workers[4] reported a dramatic use of this rearrangement when, in the course of their

reported synthesis of polycyclic aromatic compounds, the major product **8** was the result of two sequential Wagner-Meerwein rearrangements (Figure 2).

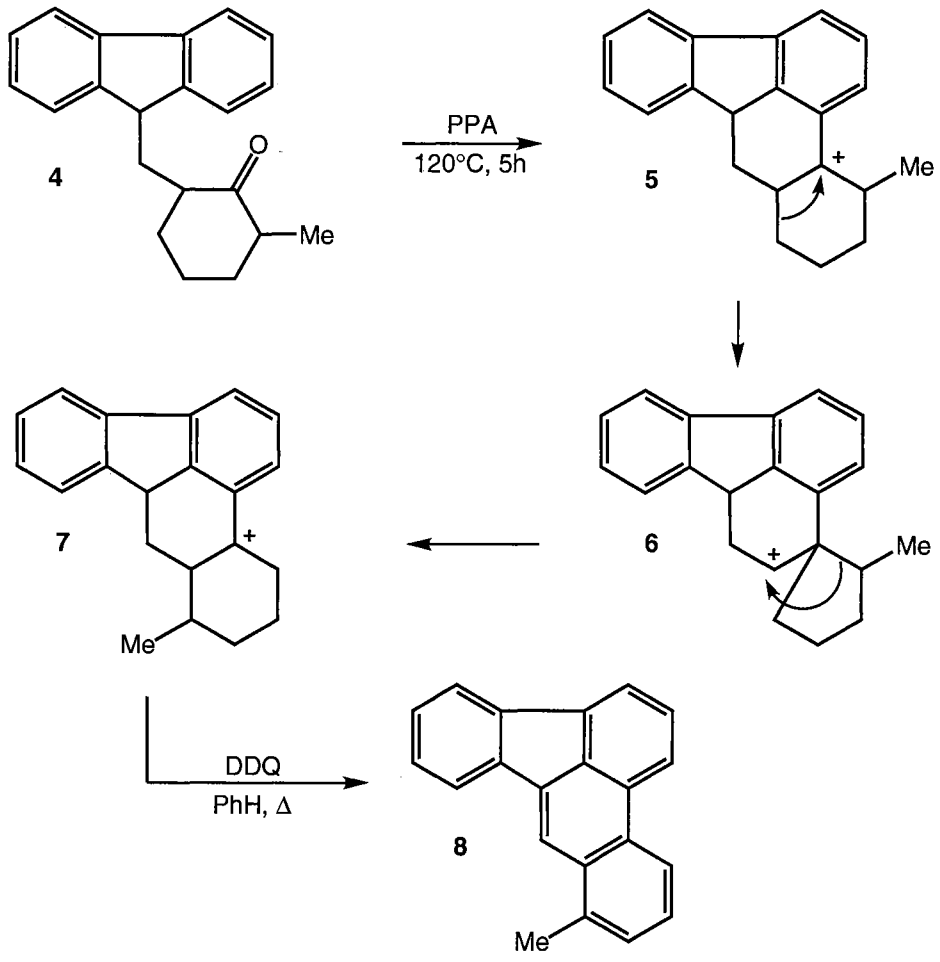
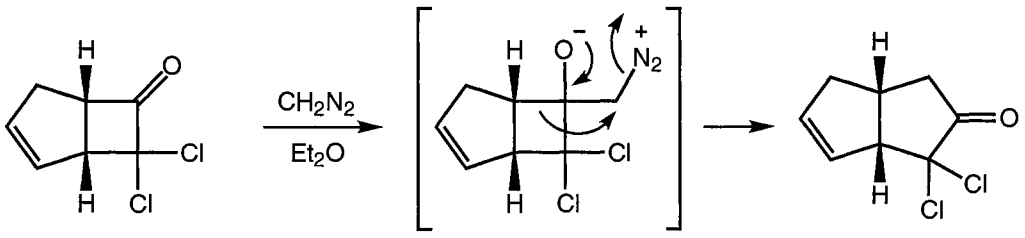


Figure 2. Double Wagner-Meerwein Rearrangement in Synthesis of Polycyclic Aromatic Compounds.

Several of the ring expansions are based on a cationic intermediate where the positive charge represents the starting point of the rearrangement. In both the pinacol and Wagner-Meerwein rearrangements the positive charge is the result of the loss of water. One notable difference in the various rearrangements is how the positive charge is generated.

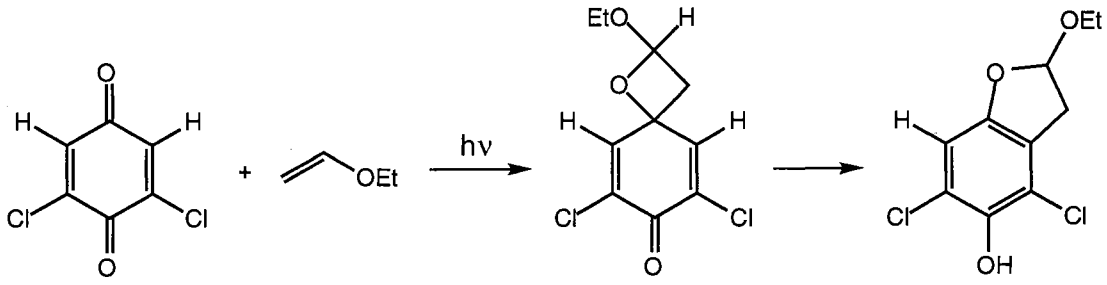
The Tiffeneau-Demjanov rearrangement utilizes the unique ability of molecular nitrogen (N_2) to serve as a leaving group. A common technique is the addition of diazomethane to a strained cyclic ketone.[5] The resulting quaternary intermediate collapses with the ring expanding and displacing the positively charged nitrogen. Green and Deprés[6] utilitized this sequence to enlarge the dichlorocylobutanone **9** to the bicyclo[3.3.0]octane **11** (Figure 3).



9 **10** **11**

Figure 3. Utilization of the Tiffeneau-Demjanov Rearrangement.

The dienone phenol rearrangement is another example of a one-carbon insertion. The driving force for this process is the formation of an aromatic ring in the final product. This rearrangement was recently utilized in a procedure that provides a novel new pathway to dihydrobenzofurans[7] (Figure 4).



12 **13** **14**

Figure 4. The Dienone-Phenol Rearrangement.

The α-ketol rearrangement represents another acid-catalyzed process. The rearrangement is an isomerization reaction of α-hydroxy ketones and aldehydes.[1] In Figure 5, a 17-α-hydroxy-20-ketosteroid yields two isomeric compounds depending on whether the reaction is run under acid (**16**) or base (**17**) catalysis.[8] The true utility of this rearrangement is the control it affords over the final products. The reaction has been extensively applied to D-ring isomerization in steroids.

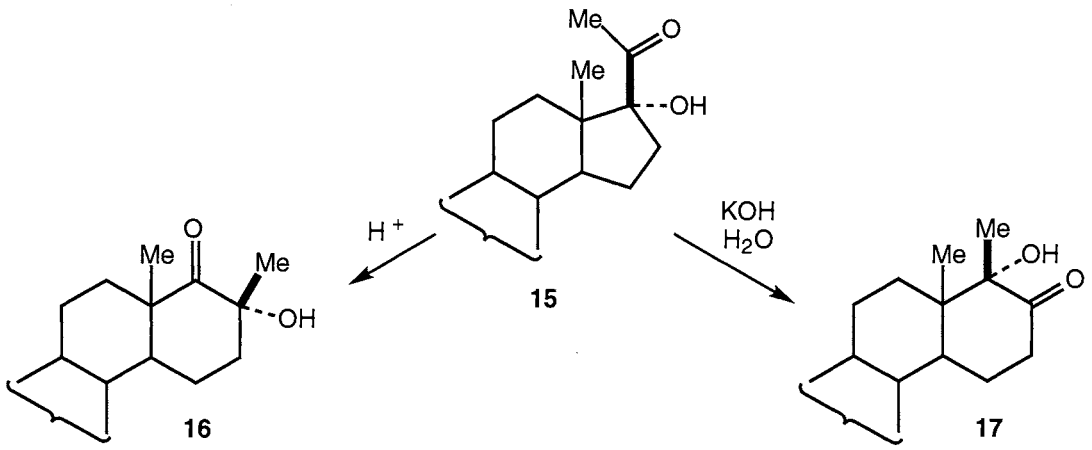


Figure 5. The α-Ketol Rearrangement.

The Wittig-Prevost method for ring expansion also represents a tandem reaction sequence. α-Tetralones can be converted to α,β-unsaturated nitriles via Wittig reaction. Prevost reaction conditions yield two ring expanded products which, when hydrolyzed under acidic conditions, give the same α-cyano ketone. This particular reaction has suffered declining popularity in the face of newer, more efficient procedures but nonetheless remains a viable entry to ring-enlarged α-cyanoketones. Geier and Hesse utilized this sequence to access α-cyanoketone **22** as illustrated in Figure 6.[9]

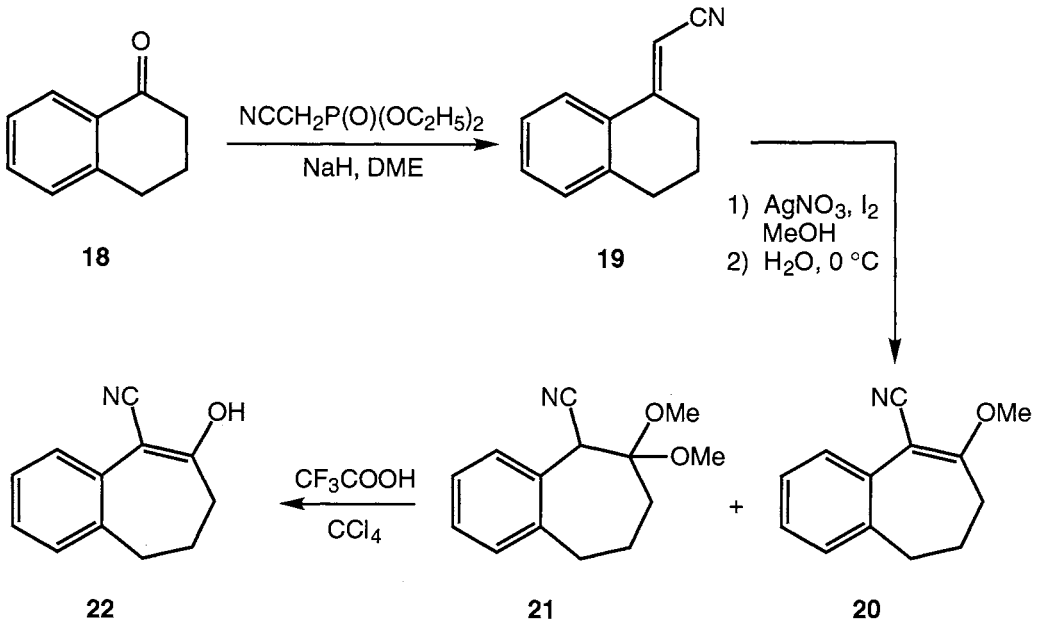


Figure 6. Synthesis of α-Cyanoketones.

Heterocyclic Rearrangements

In the previous examples, the one-carbon insertion reactions take advantage of the reactivity of the carbonyl functional group. Analogous to the carbon insertion reactions are those in which a heteroatom is inserted to the ring during expansion. The Schmidt reaction uses the carbonyl group to ultimately insert a nitrogen into the ring.[10] A recent paper[11] discusses the similarities between the Beckmann and Schmidt reactions, illustrating the specific reaction conditions that favor the Schmidt rearrangement over the other (Figure 7).

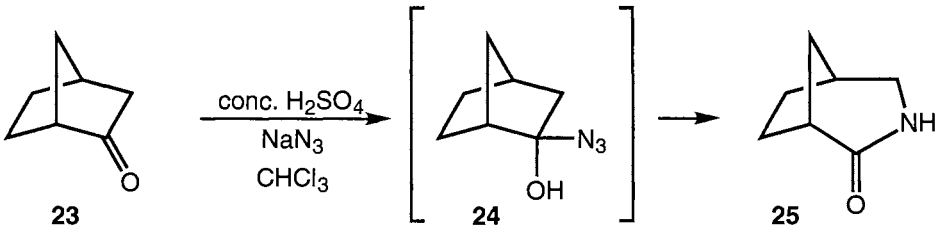


Figure 7. Schmidt Rearrangement.

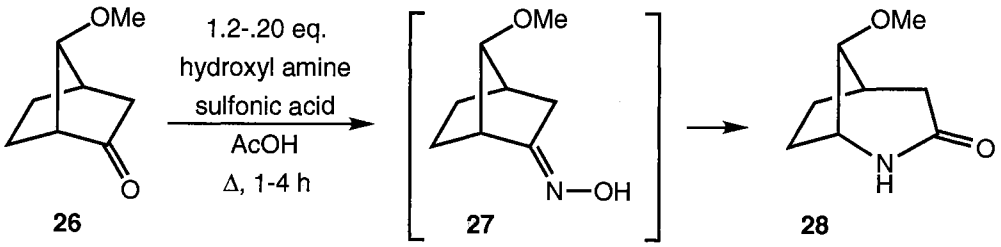


Figure 8. Beckmann Rearrangement.

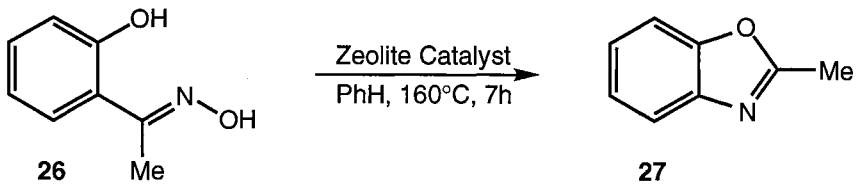


Figure 9. Catalytic Synthesis of Benzoxazoles.

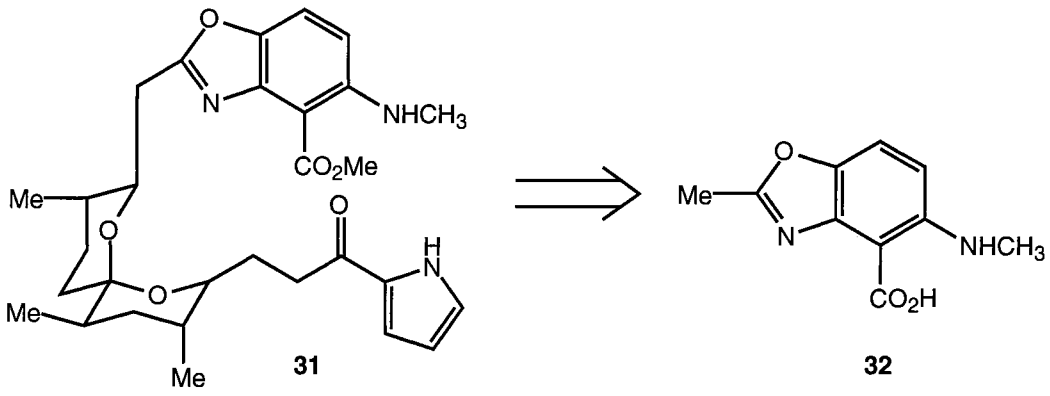


Figure 10. Synthesis of Polyethers from Substituted Benzoxazoles

Figure 8 illustrates the conditions that lead to the Beckmann rearrangement affording the major product. Another recent report, by Bhawal and co-workers,[12] describes the use of a zeolite catalyst to effect the Beckmann rearrangement of substituted oximes to benzoxazoles

(Figure 9) which are synthetically useful in the synthesis of polyether antibiotics (Figure 10) and *o*-sulfonamidophenols dye releasers for instant color photography.[13,14]

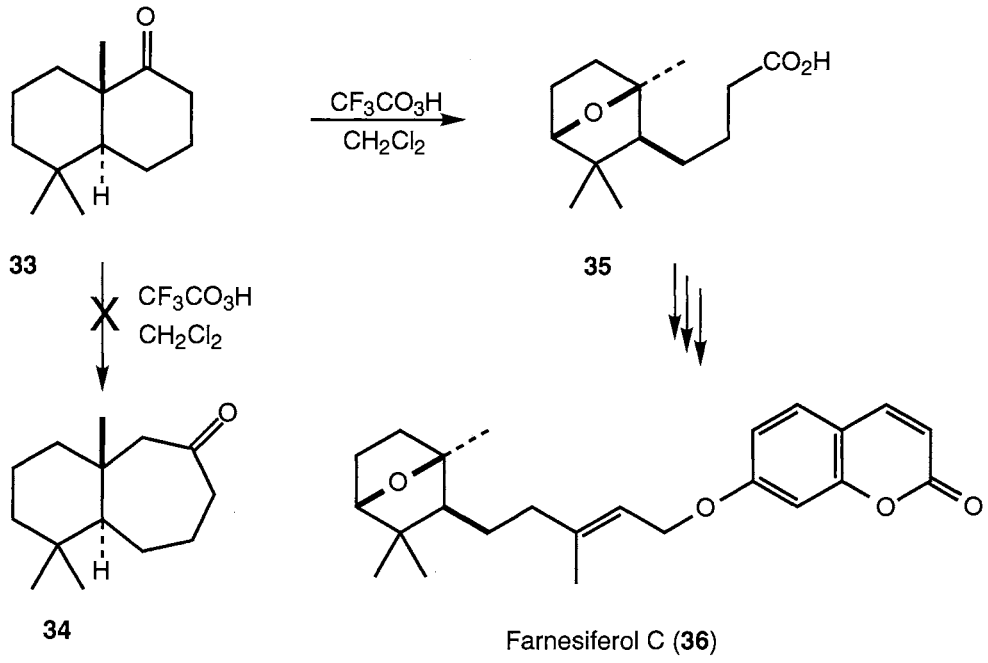


Figure 11. Formal Synthesis of Farnesiferol C.

The most well-known one-oxygen insertion reaction is the Baeyer-Villiger rearrangement. This reaction is synthetically useful in that unsymmetrical systems exhibit selectivity during rearrangement. Addition of a peroxyacid to a protonated carbonyl group generates an intermediate that rearranges by alkyl or aryl migration to displace a carboxylate from the original peroxyacid reactant. The relative migration rates of various groups has been well documented allowing for control to be achieved. Typically, alkyl groups migrate best according to the following scheme: Ph > 3° > 2° > 1° > Me. In a recent synthesis of Farnesiferol C,[15] a synthetic intermediate was obtained as the unexpected product of a Baeyer-Villiger rearrangement run in a different study. In the other study, the expected product was not formed and the rearrangement instead, yielded a completely different

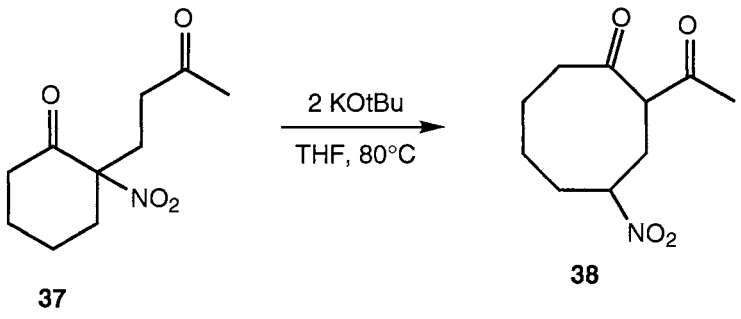
compound (Figure 11). Upon noticing the similarity between the product obtained **35** and the bicyclo[2.2.1]heptane subunit of Farnesiferol C, the researchers devised a synthesis using the serendipitously obtained intermediate. Farnesiferol C is a component of *Asa foetida* resin. The resin is considered to have sedative and vermifugal properties and is used as a spice in Iran and Afghanistan.

Ring Expansion via Side-Chain Incorporation

The nature of the side chain dictates the type of reaction involved in side-chain incorporation.[1] One type of side chain contains a terminal nucleophile which can attack a carbonyl to form a bicyclic alcohol intermediate. The possible attacking species include carbon, oxygen, and nitrogen nucleophiles. The products of these ring expansions commonly fall into one of three classes: carbocycles, lactones, and lactams.

Carbocycles via Side-Chain Incorporation

α -Nitroketones are common starting points for side chain incorporation reactions that generate ring expanded products.[16] The side chain to be incorporated is located α to the nitro group. These starting substrates are readily available via alkylation and the expansion is typically effected under basic conditions[17] (Figure 12).



37 **38**

Figure 12. Ring Expansion of α-Nitroketones.

A ring expansion that doubles as a tandem sequence is illustrated in Figure 13. A mixture of two or more different Michael acceptors in one pot can effect a ring expansion yielding a bicyclic product by a series of Michael reactions. The "MIMIRC" reaction[18] (Figure 13), involves a pair of Michael reactions followed by ring-closure.

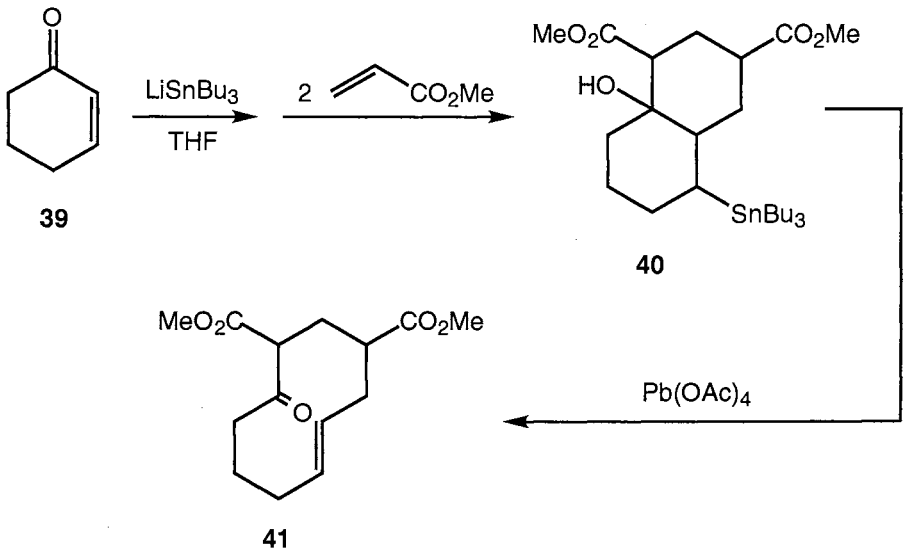


Figure 13. Ring Expansion via MIMIRC Reaction.

The MIMIRC reaction is classified as a 2+2+2 annulation. These reactions, along with many other one-pot annulations, have been the subject of a 1986 review by Posner[19] which explores several combinations of tandem reactions that result in ring expanded products.

Lactones via Side-Chain Incorporation

The use of ring expansion reactions in the synthesis of macrocyclic lactones is a well studied area. There is a large number of different naturally occurring macrocyclic

lactones, many of which possess biological activity.[20,21,22,23,24] The 2-nitrocycloalkanones that served as starting points for the synthesis of carbocycles via ring expansion can also generate macrocyclic lactones. Stach and Hesse used a 2-nitrocycloalkanone as the starting point for their synthesis of (±)-phoracantholide I **44** (Figure 14), a defense secretion of the beetle *Phoracantha synonyma.*[25]

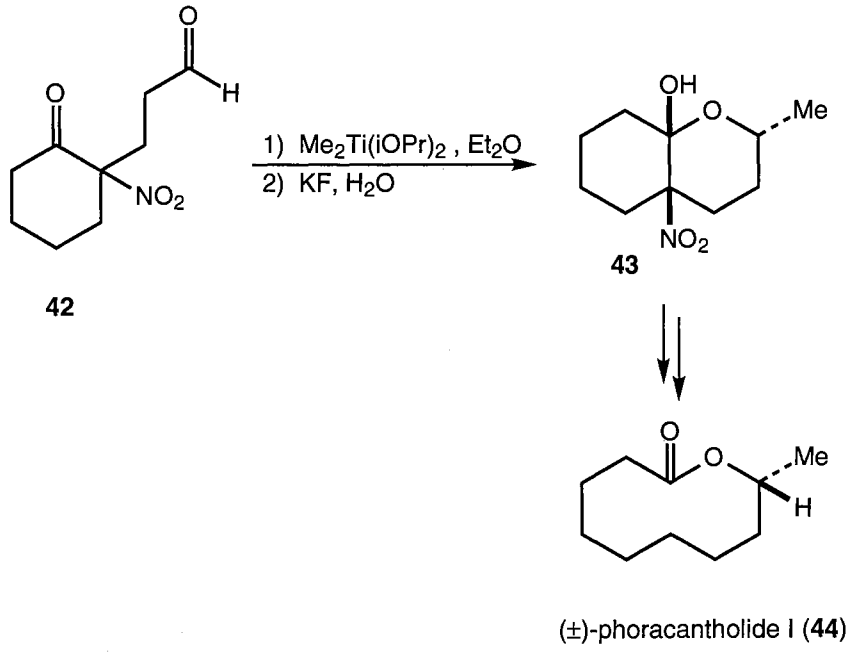


Figure 14. Ring Expansion via Lactone Formation.

Lactams via Side-Chain Incorporation

If the nucleophile in the side chain is nitrogen, then the attack on the carbonyl will result in lactam formation. An example of this reaction starts with large (10-12 membered) rings and generates larger rings incorporating the side chain. In their synthesis of

desoxoinandenine (Figure 15), Wälchli and co-workers[26] start with a 13-membered 2-nitrocycloalkanone and generate desoxoinandenine **47** which contains a 21-membered ring.

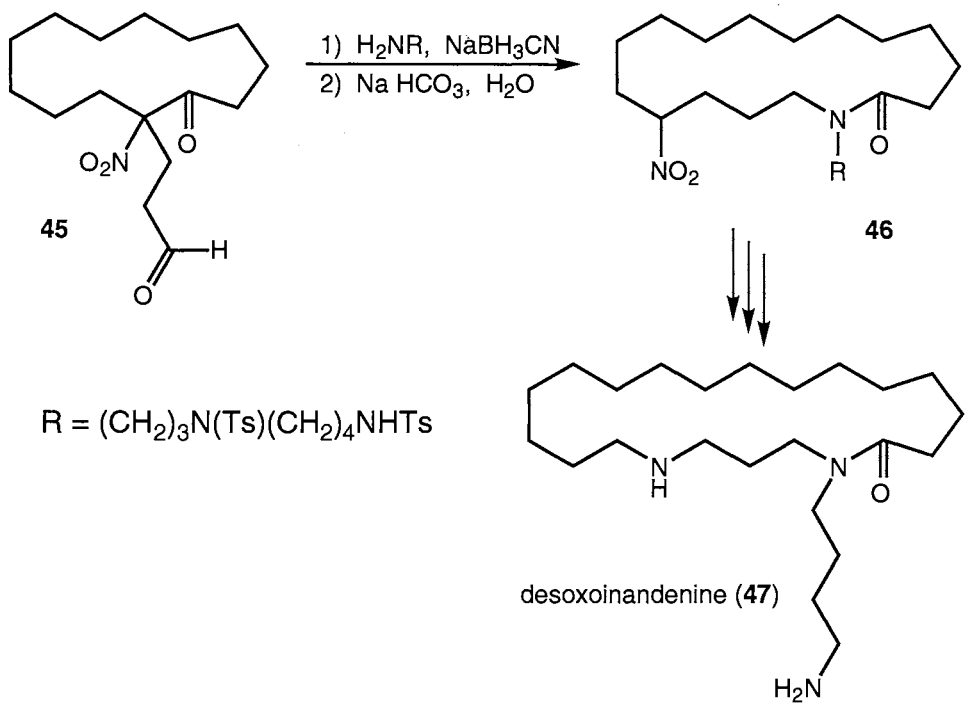


Figure 15. Synthesis of Desoxoinandenine.

Novel Unclassified Ring Expansion Reactions

The literature is rife with new applications of previously used ring expansions. Many of the new applications, however, have not been reported previously. One interesting rearrangement used twice in the recent literature[27] involves addition of *m*-CPBA to a quaternized imine (Figure 16). Protonation of the methoxy group allows the nitrogen lone pair to quaternize the amine by elimination to form the iminium ion **49**. After the peroxy chain has added to the iminium ion, the lone pair of the amine nitrogen initiates a rearrangement to afford a ring-expanded product incorporating one carbon from the peroxy

chain. Another oxidation/rearrangement using *m*-CPBA was reported in the construction of the bicyclic hydroxylamine hemiketal ring system of FR900482,[28] an anti-tumor compound (Figure 17). It is interesting to note that these reactions could be considered both a one-carbon insertion and a side-chain incorporation.

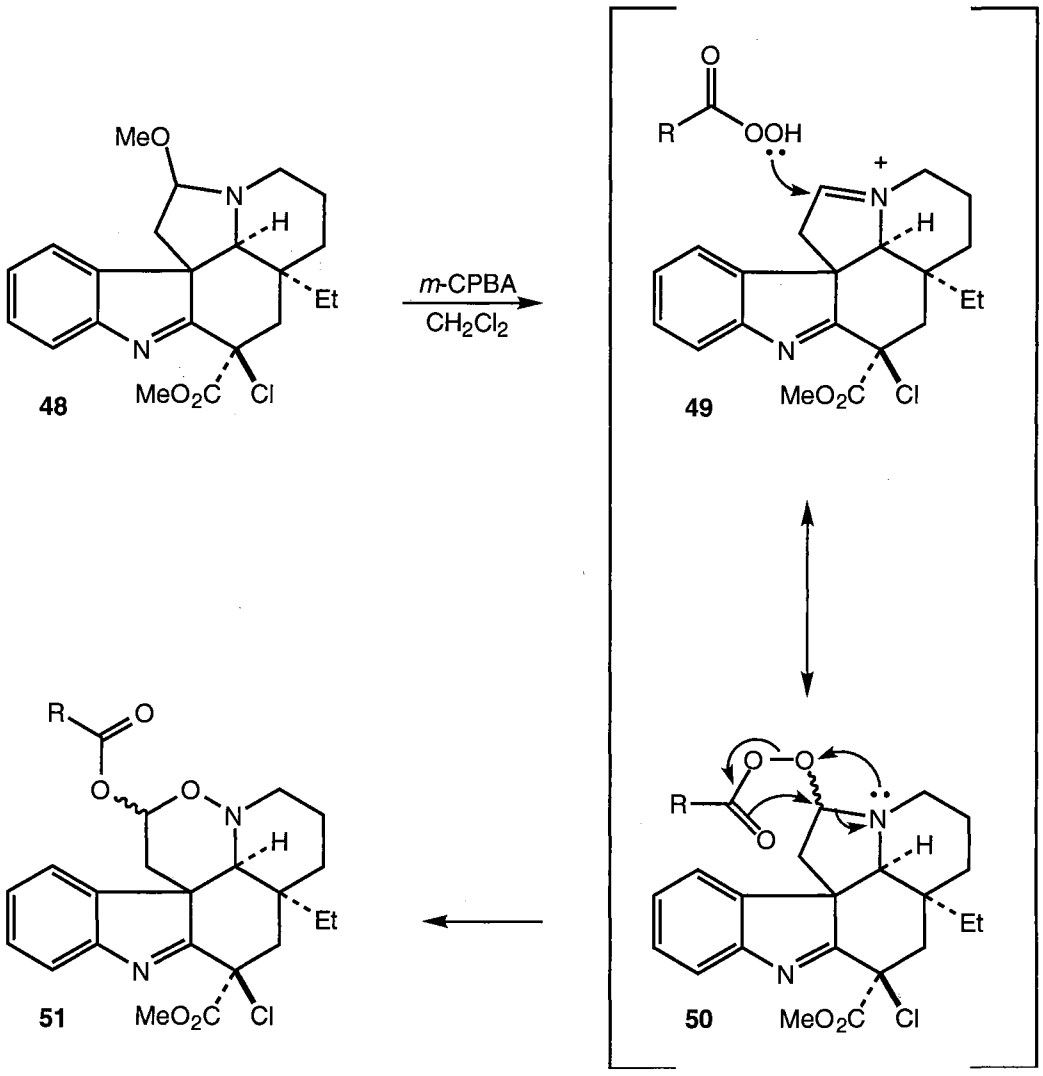


Figure 16. Oxidation/Rearrangement Reaction.

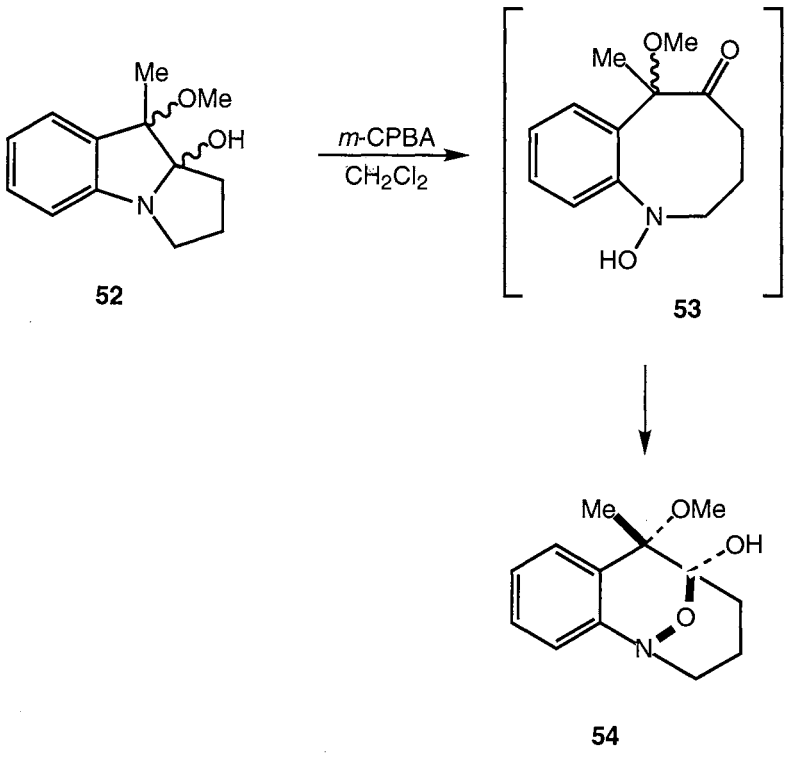


Figure 17. Construction of Bicyclic Hydroxylamine Hemiketal Ring System.

Conclusion

A vast array of ring expansion reactions are available to the modern synthetic chemist. The broad applications of these reactions allows access to unusual polycyclic and larger monocyclic systems. The ability to access these skeletons provides a stepping stone to possible medicinal compounds of the future.

Chapter 2

Historical Background: Tandem Reactions and Their Application to Organic Synthesis.

This chapter presents a general overview of the various classes of anionic tandem reaction processes. Specific attention is given to those classes which relate to the research described in this thesis. While the concept of tandem reactions is not new, recent applications to the synthesis of polycyclic systems is sparking renewed interest in these types of reactions.

Tandem reactions are known by many monikers;[29] cascade, consecutive, domino, iterative, one pot (or one flask), sequential, and zipper reactions. Typically, a tandem process links several transformations together in one reaction flask. Usually, an initial reaction produces an intermediate that can further react with one or more strategically placed functional groups. The intermediate generated is not limited to intramolecular in situ reactions. The intermediate can react with centers in the same molecule, centers in other molecules, or even with reagents added after the initial transformation takes place.

Tandem reaction processes represent an improvement over many procedures in that the overall synthetic efficiency increases by virtue of the lower number of laboratory operations required and also reduced quantities of starting materials and solvent.[30] One highly desirable trait of tandem reactions, namely their ability to access unique cyclic systems, often with high selectivity, has increased the utility of tandem processes for the preparation of novel polycyclic systems.

Classification of the various types of tandem reactions has not been standardized. Logical systems have been advanced in several recent review articles.[19,29,31] These articles assort the tandem reactions by the type of intermediate produced,[30] or the name reactions involved the first two steps of the synthesis.[31] There is also a system that classifies the reactions based on the number of carbons in each subunit involved in the reaction.[19] One school of thought divides the so-called "one-pot" reactions into two classes, domino reactions and consecutive reactions. A domino or cascade reaction, hereafter referred to as a tandem reaction, is a process involving two or more sequential transformations in which the later reactions occur as a result of functionalities or reactive centers generated by the initial reactions.[32] Simple generation of a reactive intermediate, i.e. deprotonation to an anion, doesn't qualify as a reaction step. A consecutive reaction involves adding another reagent or catalyst after the initial intermediate is formed and, without isolation, a subsequent reaction gives the final desired product.[30] The tandem reaction definition is then further divided according to the transformations occurring in the sequence. The two common classification methods center around the type of intermediate involved or simply using the names of the reactions involved. To that end, an incomplete list of the transition state types might include cationic, anionic, radical, and carbene. A discussion of all the documented reactions involved is far too sizeable to be considered here. This survey will thus focus on anion-mediated processes.

A survey of the literature indicates that in most tandem reactions, the first two transformations are of the same type with anionic-anionic processes being the most common.[30] It should also be noted that the common characteristic of tandem reactions involves the second and subsequent steps occurring intramolecularly. The majority of anionic tandem reactions are initiated by deprotonation of an activated carbon to form a carbanion which reacts with a suitable functional group to generate a new anionic center. This represents the first step of the tandem sequence. The new anionic intermediate is then free to attack another suitably disposed reactive site in either inter- or intramolecular

fashion. The anionic processes are typically terminated by reaction with an electrophile (acid workup) or elimination of a suitable leaving group.[29]

When considering the anionic-anionic tandem reactions, those involving Michael additions are the most frequently encountered in the literature.[29,30] These processes excel in the synthesis of polycylic systems. The skeletons for precursors to sesquiterpenoids, namely bicyclo[2.2.2]octane and tricyclo[5.3.1.0]undecane, are easily accessed by Michael-Michael sequences as shown in the synthesis of seychellene **6** (Figure 1).[33]

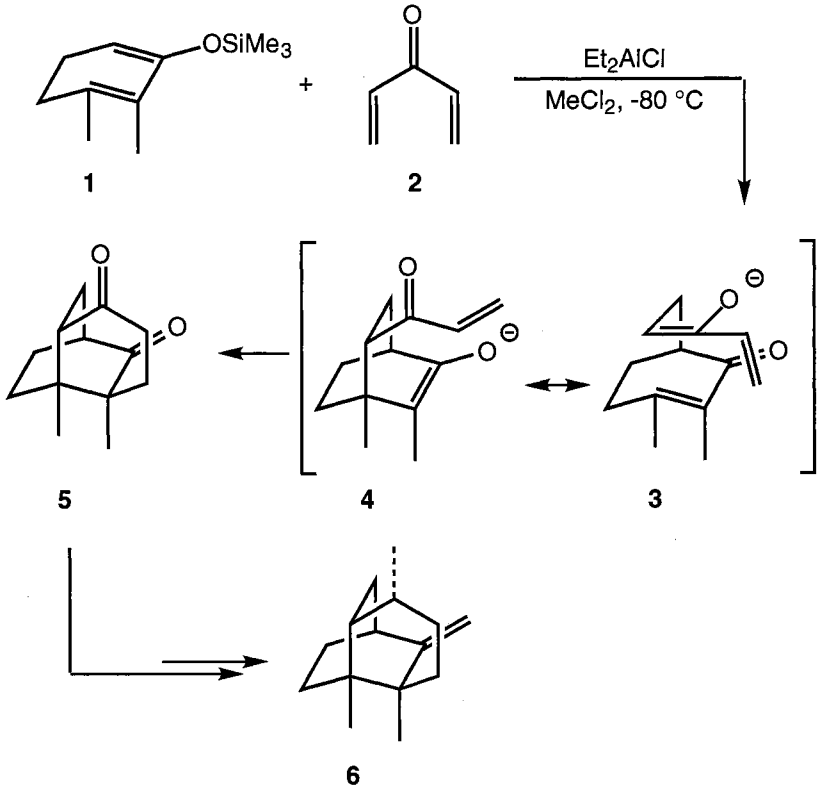
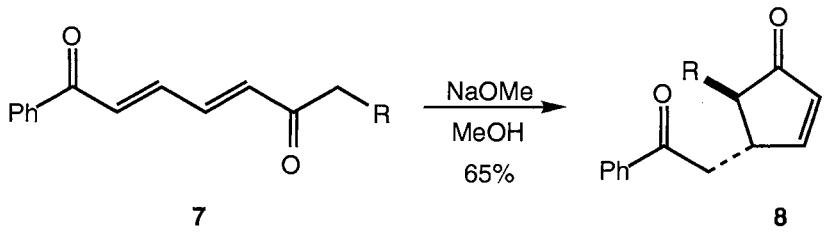


Figure 1. Synthesis of Seychellene.

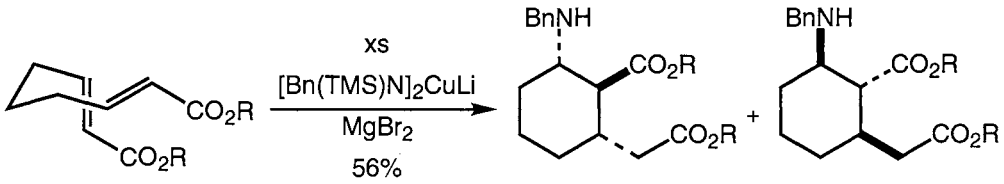
If the elegance of the Michael-Michael sequence is illustrated by the formation of complex polycyclic systems, it's utility can be seen in the synthesis of simpler carbocycles. Ong and co-workers[34] developed a simple pathway to substituted cyclopentenones (Figure

2). Initial 1,4-addition of methoxide to the α,β-unsaturated alkyl ketone **7** generates an anion which can undergo proton exchange and then close on the α,β-unsaturated aryl ketone. Base-induced loss of methoxide installs the double bond to yield the cyclopentenone derivative **8**.



7 **8**

Figure 2. Monocyclic Carbocycles via Tandem Reactions.



9 **10** (91:9) **11**

Figure 3. Enhanced Enantioselectivity of Tandem Reactions.

Many of the tandem Michael-Michael reactions exhibit significant stereoselectivity. This technique was illustrated by Shida and co-workers[35] in the synthesis of a series of highly functionalized cyclohexanes. The use of lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) to effect tandem conjugate additions of diesters has been reported. Using the "cuprate" of LSA in the presence of a bidentate chelating Lewis acid markedly increases the diastereo- and enantioselectivity (Figure 3).

The initial anionic species can also be generated by more elegant means than deprotonation. Figure 4 illustrates a palladium-catalyzed dealkoxycarbonylation[36] that

results in the π-allylpalladium complex **13** which then adds in Michael fashion to form the spirane product **14**.

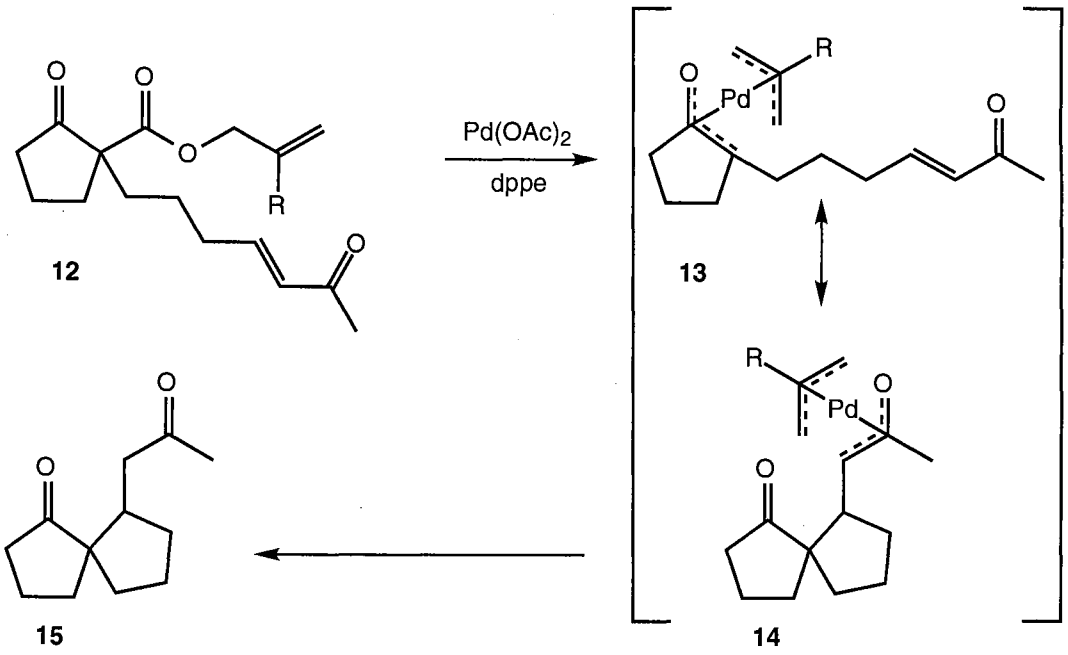


Figure 4. Palladium-Catalyzed Formation of Initial Anionic Species in a Tandem Reaction.

Other methods of generating the initial anionic species include desilylation via fluoride ion, reduction by sodium amalgam, retro-aldol fragmentation, and the following example[37] (Figure 5) in which oxidation of **15** using Ag_2O results in the formation of the spirocyclic fused compound **18**. The exact mechanism is unclear but oxidation of **15** results in the benzoquinone intermediate **16** which cyclizes via C-alkylation of the side chain onto the enone system of the benzoquinone, rearomatizing the compound to the spirocyclic intermediate. A second oxidation by Ag_2O results in the 1,4-benzoquinone derivative **18**.

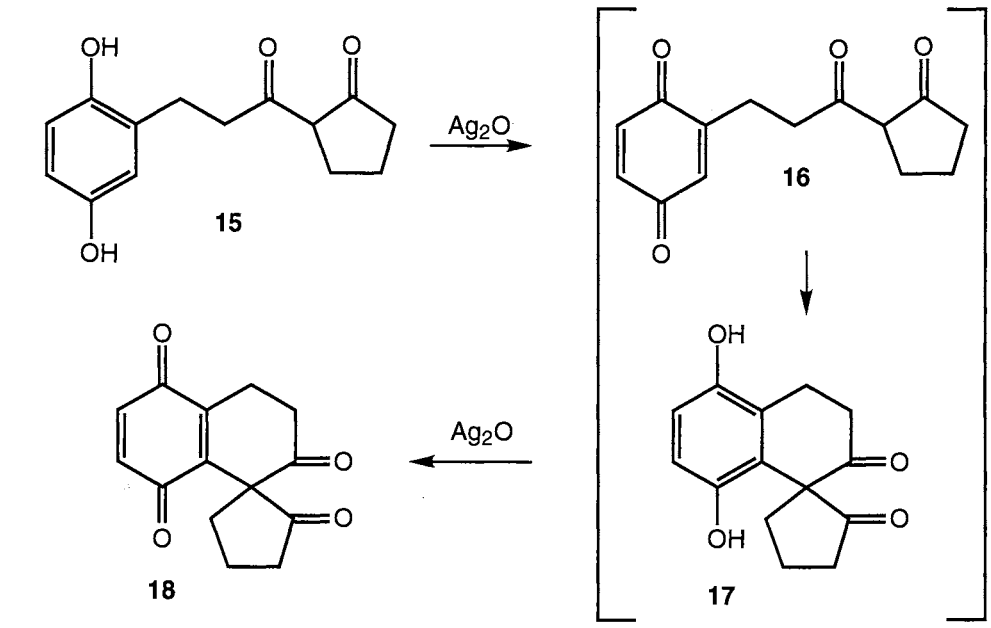


Figure 5. Oxidation/Ring Closure Tandem Reaction.

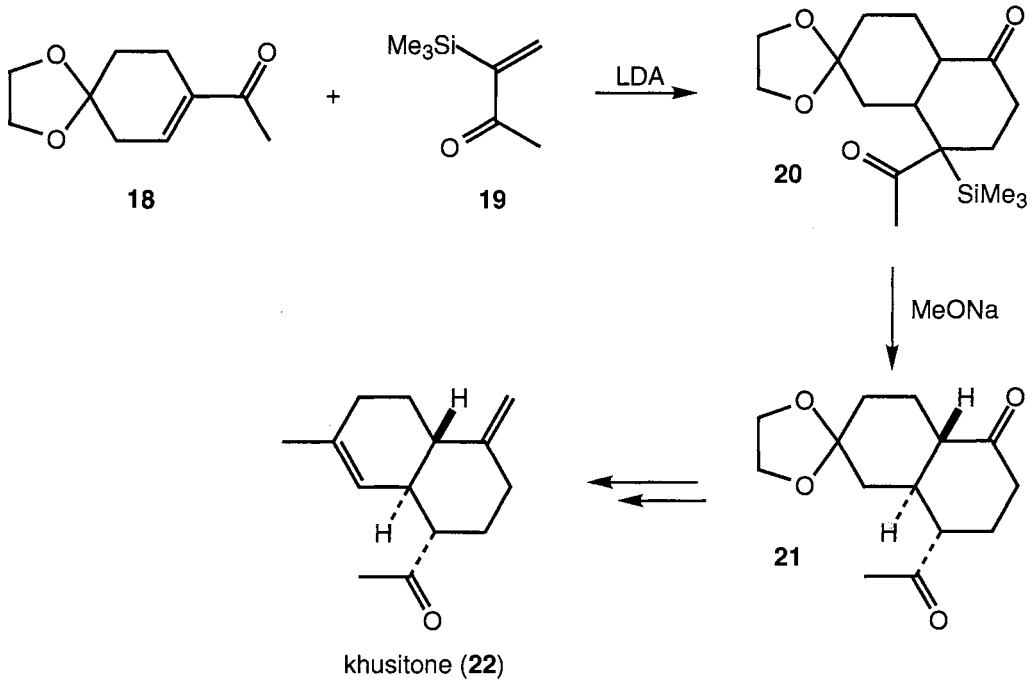


Figure 6. Reflexive Michael Reaction in the Synthesis of Khusitone.

A special case of a Michael-Michael tandem is known as a reflexive Michael addition. In reflexive Michael reactions each reactant serves as both acceptor and donor with the second part of the reaction forming a six-membered ring. These reactions are complementary to the Diels-Alder sequence but the reflexive Michael addition has certain advantages such as lower reaction temperatures and fewer side reactions to lower the yield. In Figure 6, Hagiwara[38] demonstrates the superiority of using the reflexive Michael reaction, over the lower yield pathway that utilizes the Diels-Alder cycloaddition, in the synthesis of khusitone.

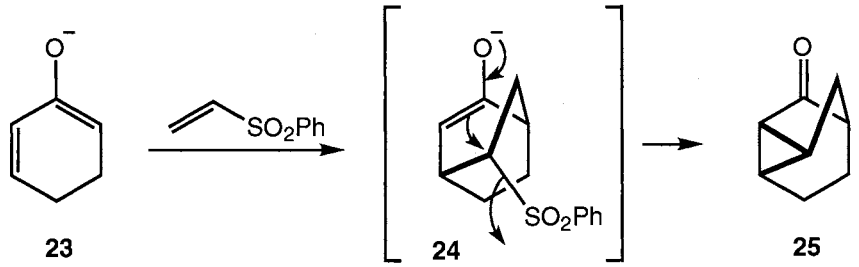


Figure 7. MIMIRC Reaction in Tricycle Synthesis.

A tandem process that combines another transformation with two Michael additions is the Michael-Michael-ring closure (MIMIRC) reaction.[19] In the following sequence (Figure 7), Cory and co-workers[39] applied this MIMIRC protocol to the synthesis of tricyclo[3.2.1.$0^{2,7}$]octan-6-one **25**. The tricyclo[3.2.1.0]octane system is an integral structural element of the ishwarane and cycloseychellene families of sesquiterpenes, as well as the trachylobane and helifulvane families of diterpenes.

The flexibility of the Michael reaction with respect to tandem reactions is witnessed by it's ability to pair with several other reactions. Probably the earliest recorded tandem reaction was the Robinson annulation[40] which is effectively a Michael-aldol sequence.

Stork and co-workers[41] took advantage of stereoselectivity exhibited by the Robinson annulation to construct a synthon for the CD-ring of cortisone, which was subsequently carried on to the title compound **28** (Figure 8).

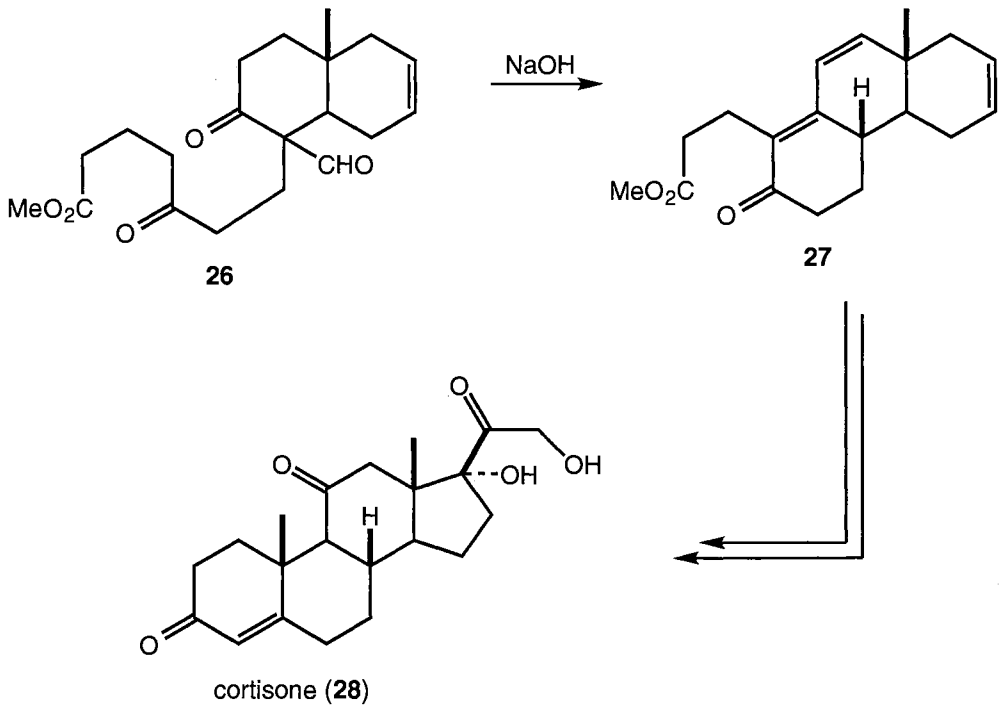


Figure 8. Use of the Robinson Annulation in the Synthesis of Cortisone.

In a classic adaptation of the Robinson annulation,[42] Stork took advantage of the nucleophilic character of enamines and used them to start the tandem reaction. Starting with the enamine **29**, he utilized this approach in the assembly of the DE-rings of yohimbine **34** (Figure 9).

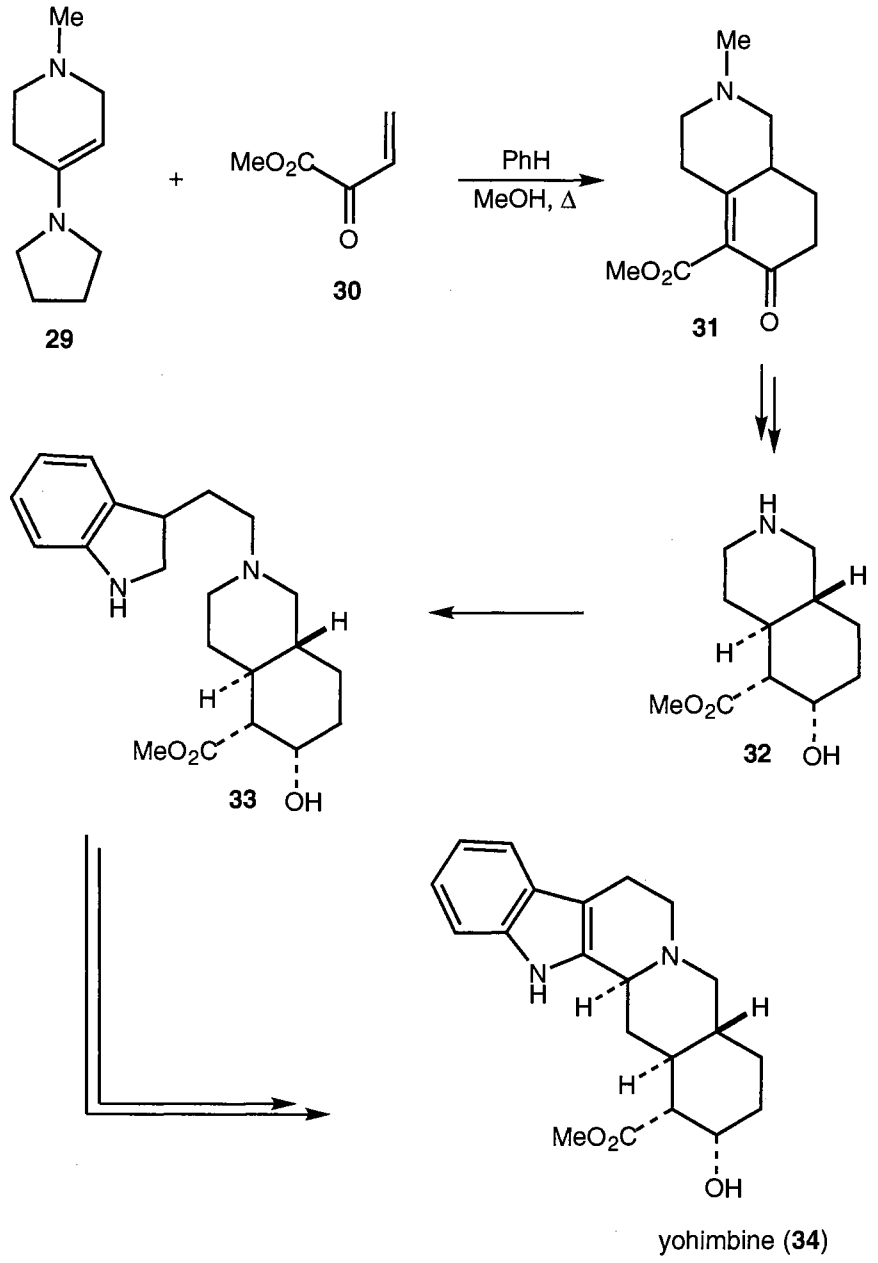


Figure 9. Stork Synthesis of Yohimbine.

Similar to the Robinson annulation, the Dieckmann cyclization can also be paired with the Michael addition to form another tandem process. Tarnchompoo[43] used the tandem Michael-Dieckmann reaction to form the key intermediate **36** in the total synthesis

of diospyrol **37** (Figure 10). Diospyrol is a potent anthelmintic from *Diospyros mollis* and is widely used in southeast Asia, especially Thailand.

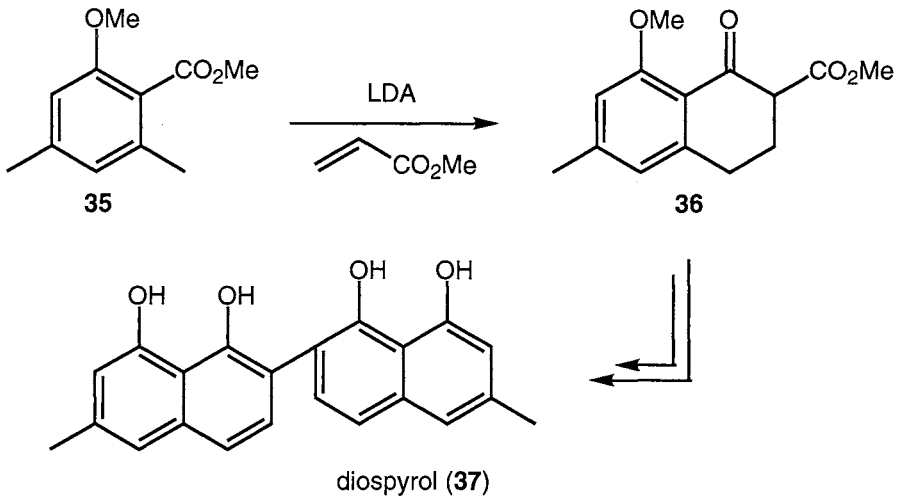


Figure 10. Synthesis of Diospyrol.

Another tandem reaction that provides an alternative to the Diels-Alder is the pairing of the Michael addition and the Wittig reaction. In the majority of these processes, the Michael reaction initiates the tandem sequence with the Wittig olefination anchoring the pair by typically closing a ring.[44] This tandem process was utitilized by Kuehne[45] in synthesizing the key cyclohexenecarboxylic ester intermediate **39** in the pathway to ibogamine **41** (Figure 11). Ibogamine is a member of the Iboga group of alkaloids. While chemically interesting in terms of structure, this class of alkaloids expresses intriguing pharmacological activity. The central nervous system activity of ibogamine parallels that of ibogaine which is used by African natives as a stimulant to combat sleep and hunger. Other iboga alkaloids are synthetic and biosynthetic precursors to anhydrovinblastine and antineoplastic vinblastine. Alternative approaches to the key intermediate, i.e. Diels-Alder

cycloaddition or reduction of the appropriate aromatic compound proved unfeasible, necessitating the use of the tandem Michael-Wittig methodology.

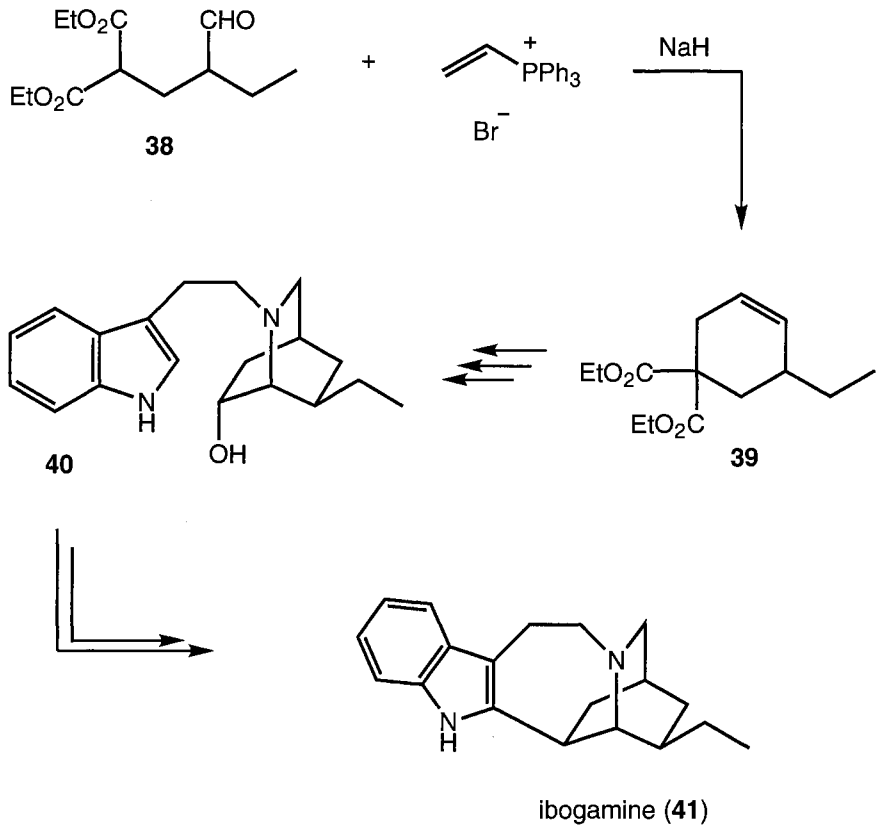


Figure 11. Synthesis of Ibogamine.

The Michael reaction can also serve as a termination step in a carbopalladation-termination tandem process.[46] The carbopalladation products of many π-compounds are thermally stable and considered "living". These "living" carbopalladation reactions can be terminated by combination with several reactions.[46] In their synthesis of $\Delta^{9(12)}$-capnellene[47] (Figure 12), Balme and Bouyssi utilized an intromolecular Michael addition to the palladium-double bond complex **43** to terminate the carbopalladation reaction. This led to the tricyclic intermediate **44** that was carried on to the title compound **45**.

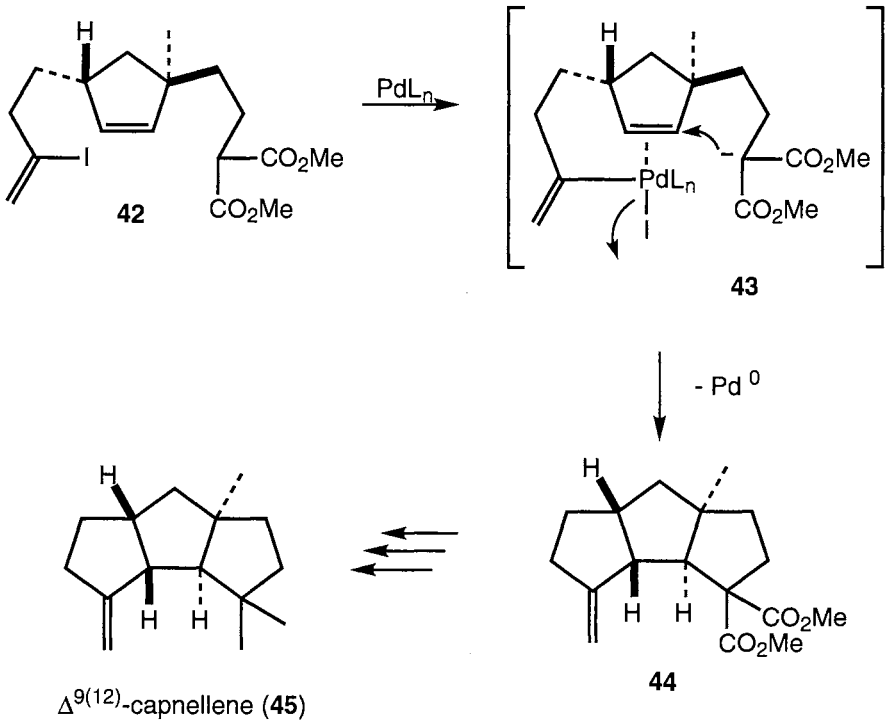


Figure 12. Synthesis of $\Delta^{9(12)}$-Capnellene.

Recent studies[48] in the application of tandem sequences using samarium iodide (SmI_2) illustrated several processes where radical/anionic and anionic/radical tandem reactions were used. SmI_2 is an ether-soluble one-electron reducing agent. It promotes a host of useful transformations[48] including radical cyclizations, ketyl-olefin coupling reactions, pinacolic coupling reactions, Barbier-type cyclizations, aldol-type reactions, etc. SmI_2 also exhibits an unusual selectivity in these reactions and that selectivity can be modified by altering solvents,[49] reaction conditions, or adding catalysts.[50] The radical/anionic processes are the most thoroughly studied of the tandem sequences promoted by SmI_2, allowing access to a variety of polycyclic systems.[48] In Figure 13, the unsaturated ketohalide **46** was suitably disposed for cyclization via the radical formed by reduction with SmI_2. The resulting cyclic radical **47** was reduced a second time to the

enolate anion **48** which was then trapped by the electrophile to produce the bicyclo[3.3.0]octane derivative **49**.

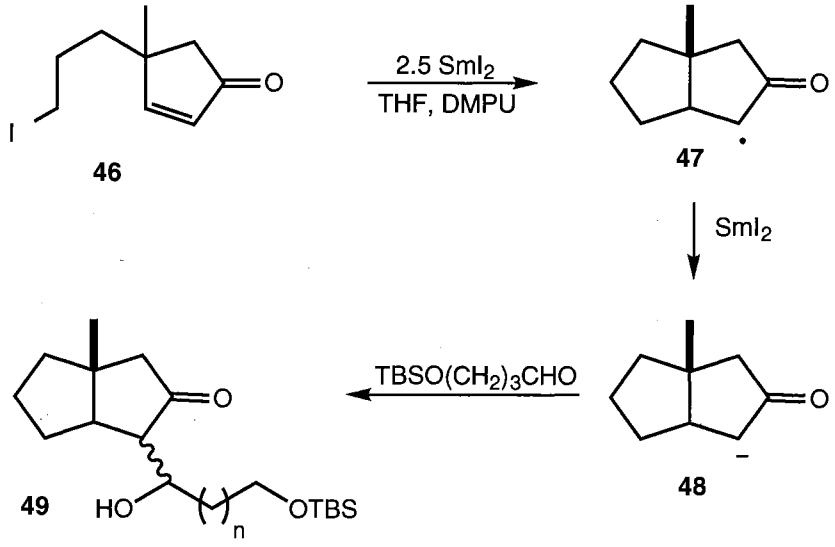


Figure 13. Tandem Radical/Anionic Reaction Using SmI_2.

Similarly, the anionic/radical process is also utilitarian in it's ability to access complex polycyclic systems. This class of sequential reactions are represented by ketyl olefin cyclizations which are preceded by nucleophilic acyl substitutions. The addition of an electrophile sets up an anionic/radical/anionic tandem sequence.[51] In Figure 14, iodoester **50** undergoes an SmI_2 mediated anionic intramolecular acylation reaction. SmI_2 then generates the ketyl **51** which cyclizes on the olefin yielding a cyclic radical which, after a final SmI_2 reduction, affords the anion **52** that is ultimately trapped by acetone to yield the bicyclo[4.3.0]nonane derivative **53**.

The use of SmI_2 can also effect a tandem anionic-anionic process. This process manifests itself as either a pair of Barbier-type cyclizations or a nucleophilic acyl

substitution followed by a Barbier-type cyclization. In a recent work[52] the latter of the two tandem sequences is exploited to afford bicyclic and tricyclic systems. In Figure 15, the diiodocyclopentane derivative **54** initially undergoes an intramolecular acyl substitution reaction to afford the ketone **55**. Subsequent Barbier cyclization gives the tricyclic product **56**. The substitution pattern in the final product can be governed by the selective rate of reduction by SmI_2. Alkyl iodides are reduced preferentially over alkyl chlorides[48] and this bias allows for selective reaction of one chain before the other. This strategy also provides a viable entry into seven- and eight-membered ring systems.

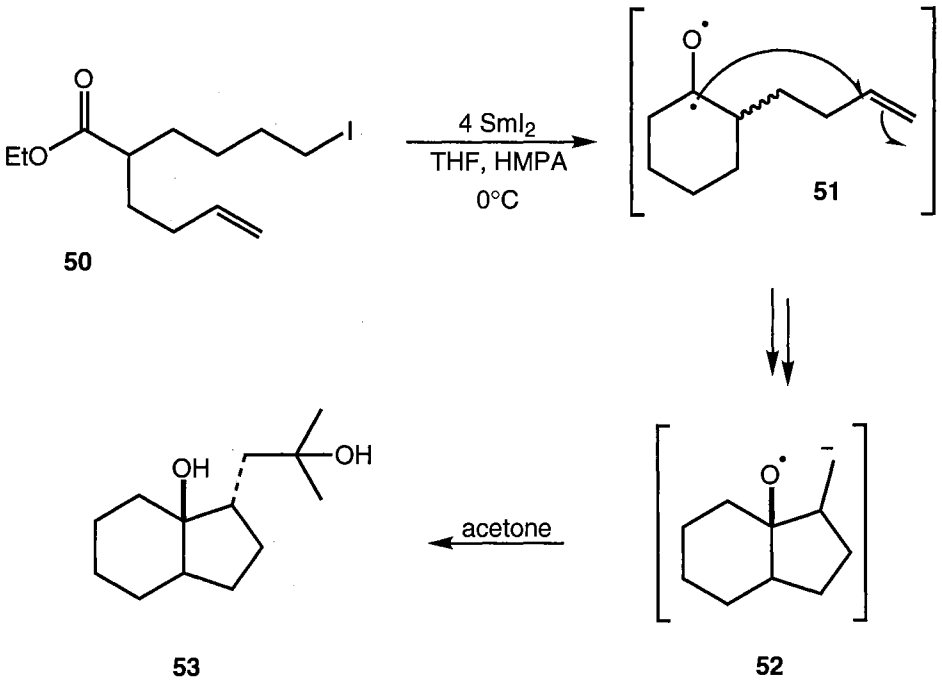


Figure 14. Tandem Anionic/Radical/Anionic Reaction Using SmI_2.

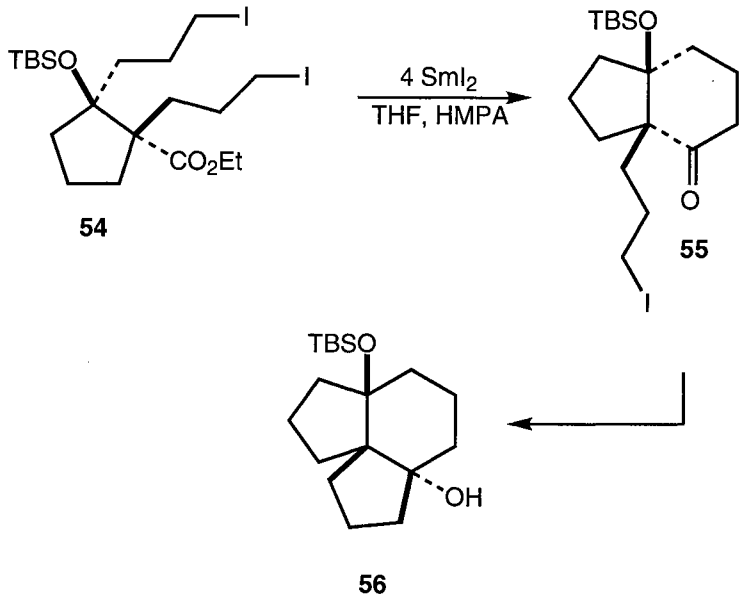


Figure 15. Tandem Anionic/Anionic Reaction Using SmI_2.

Conclusion

The recent literature[29,30,32,48,53] clearly establishes the broad utility of tandem reaction processes. While much work has already been done there remains a plethora of unexplored possibilities. The work performed in this study is but a small contribution to the expanding knowledge of tandem reactions. With target molecules and key intermediates becoming increasingly complex there is a great need for reaction sequences that are capable of forming more than one bond per reaction step. Additionally, the ever-tightening government regulation of research favors those reactions that are highly efficient while maintaining a low chemical waste/product ratio. Fortuitously, the afforementioned are key characteristics of tandem reactions, leaving little doubt about the logic of expanding the synthetic applications of such processes in the future.

Chapter 3

Historical Background: Ring Closures by Tandem Dealkoxycarbonylation-Michael Addition Reactions

Introduction

This chapter will present a general overview of the tandem dealkoxycarbonylation-Michael reaction and it's application to the synthesis of various cyclic compounds. This particular tandem sequence is relatively new and the majority of references in the literature pertain to work done in our laboratory. Earlier work that led to the development of this sequence will be considered with emphasis on recent and current projects that continue to contribute to this area of synthesis.

Earlier Work

Prior to the development of the tandem dealkoxycarbonylation-Michael addition reaction, there was considerable work done on tandem sequences where one of the reactions was a Michael addition. A highly stereoselective tandem Michael-Michael sequence (Figure 1) was developed that generated both mono- and fused systems.[54] Conjugate addition of the triester enolate **2** to the enone **1** generated the enolate intermediate **3** which underwent intramolecular cyclization to afford the cyclic triester product **4**.

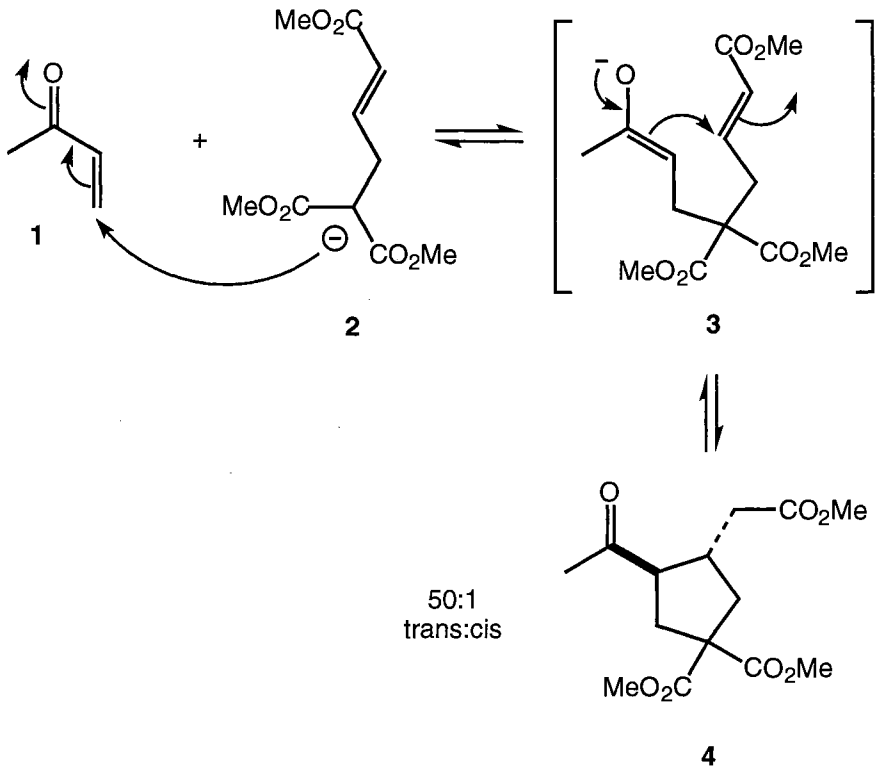


Figure 1. Tandem Michael-Michael Reaction.

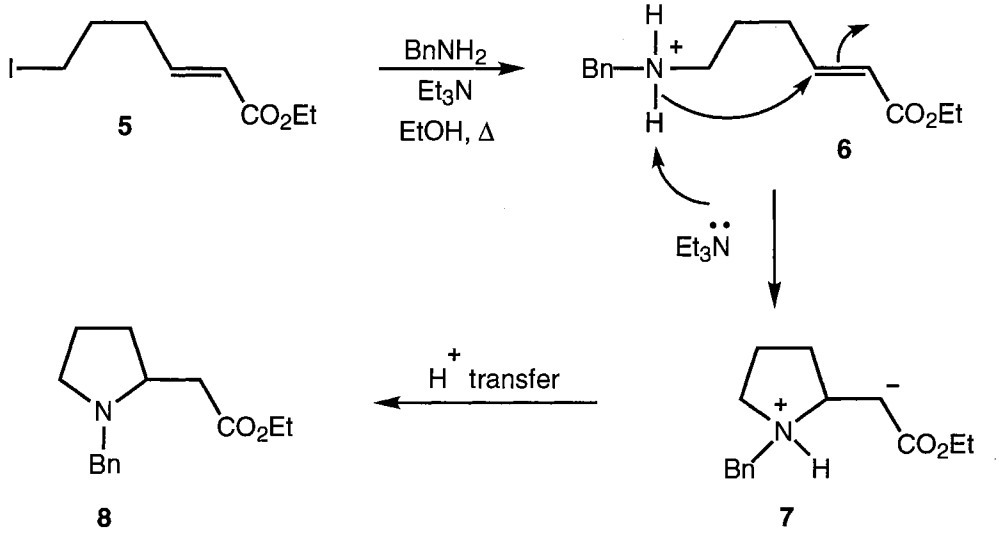
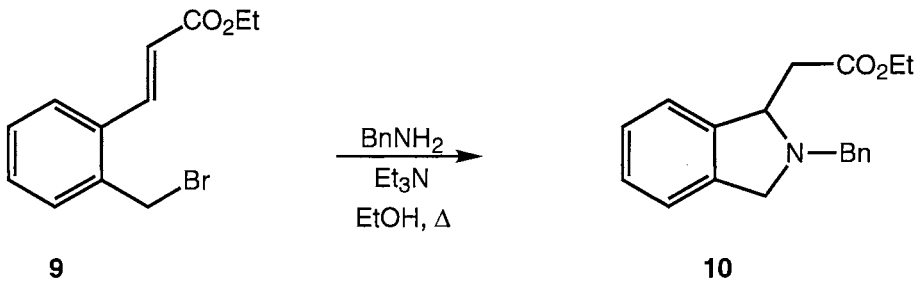


Figure 2. Tandem S_N2-Michael Reaction.

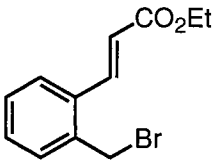
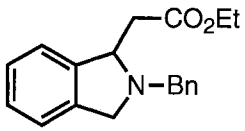
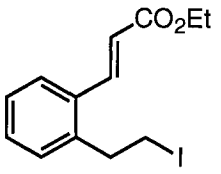
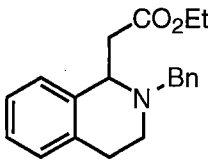
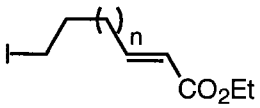
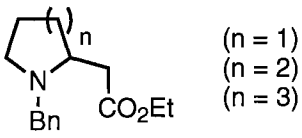
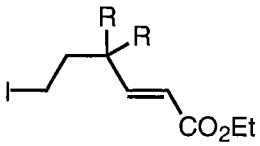
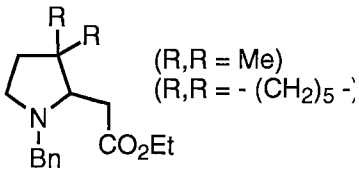
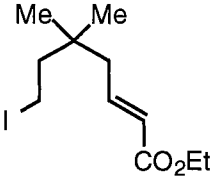
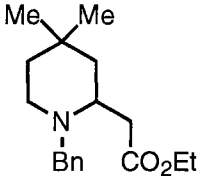
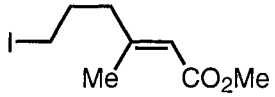
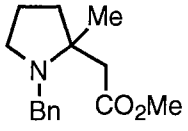
The study of tandem sequences involving Michael reactions was continued with the development of a tandem S_N2-Michael addition reaction[55] (Figure 2). Selection of an appropriate substrate **5** allowed for the nucleophile ($BnNH_2$) to first effect an S_N2 displacement to form the quaternary intermediate **6**. Deprotonation of the quaternary nitrogen set up the Michael addition to the activated double bond, and subsequent proton transfer afforded the cyclic product **8**. Following the initial success of the tandem S_N2-Michael with monocyclic products the sequence was applied to polycyclic precursors that contained aromatic functionality. Thus, the aromatic precursor **9** was readily converted to the aromatic heterocycle **10** (Figure 3).



9 **10**

Figure 3. Fused Ring Heterocycles via Tandem S_N2-Michael Reactions.

Encouraged by the continued success of the S_N2-Michael addition tandem, several classes of possible cyclization substrates were considered. The reaction protocol was applied to those substrates showing potential and eventually a series of cyclization substrates, encompassing both monocyclic as well as fused heteroaromatic systems, were cyclized. Table 1 summarizes the results of a number of S_N2-Michael addition reactions.

Substrate	Nitrogen Heterocycle	Yield (%) [a]
		69
		--[b]
	 (n = 1) (n = 2) (n = 3)	63 59 <5
	 (R,R = Me) (R,R = - $(CH_2)_5$ -)	64 68
		66
		71

[a] Yields refer to isolated products. [b] Elimination was observed to give ethyl (*E*)-3-(2-ethenylphenyl)propenoate.

Table 1. Results of Nitrogen-Initiated Tandem S_N2-Michael Addition Reactions.

With the efficiency of nitrogen as a nucleophile established, the next logical step was to consider another heteroatom whose lone pair imparted nucleophilic character.

Sulfur was a likely candidate and studies were conducted to identify a reagent that could effect the initial S_N2 reaction. Thiourea was tested as a potential nucleophile.[55] In Figure 4, thiourea attacks bromoester **11** to generate the isothiouronium salt **12**. Neutralization of the salt using NaOH gives the thioamidine **13**. Subsequent hydrolysis of the thioamidine generates a thiolate anion which adds in Michael fashion to the acrylate moiety to afford the sulfur heterocycle **14**.

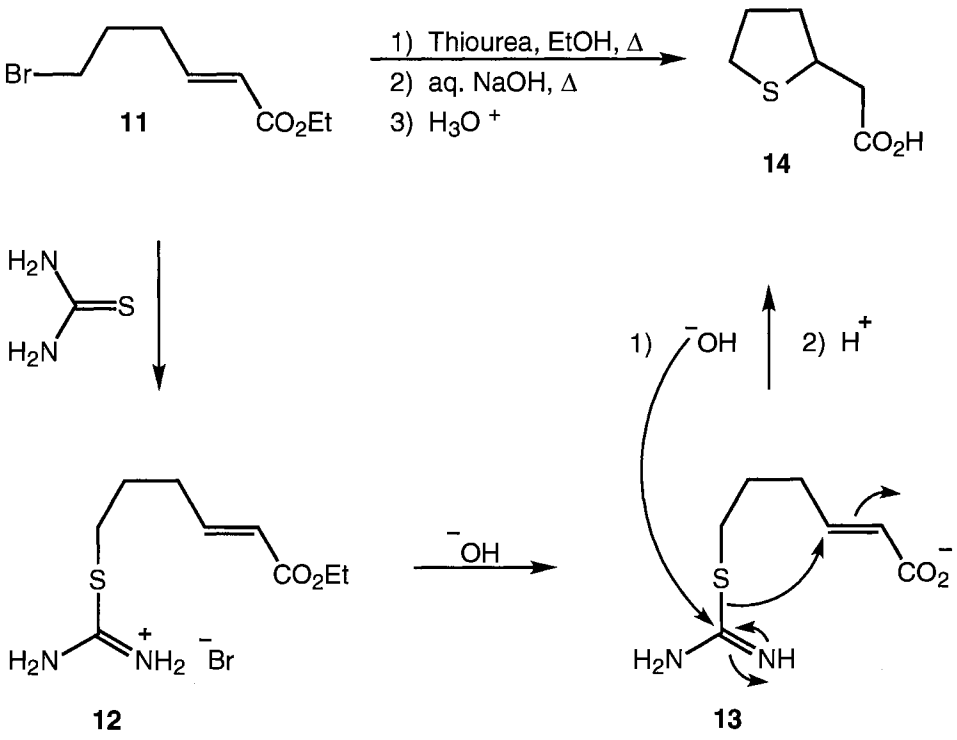
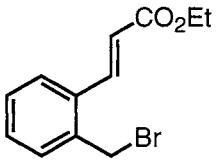
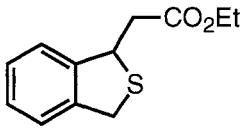
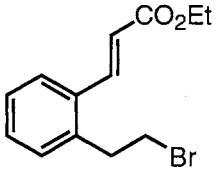
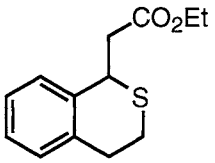
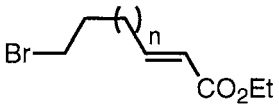
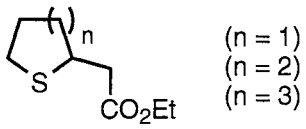
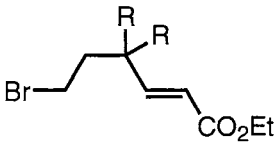
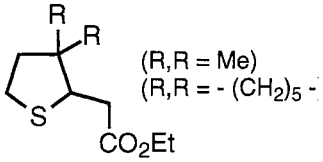
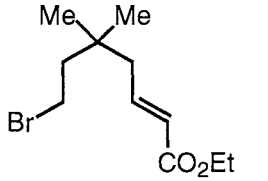
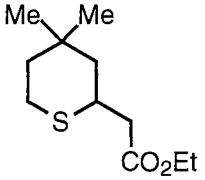
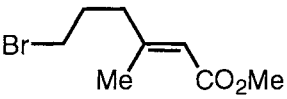
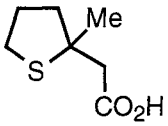


Figure 4. Tandem S_N2-Michael Addition Reactions Using Sulfur as a Nucleophile.

Initial reactions using thiourea were successful and various classes of substrates were evaluated as potential cyclization candidates. Ultimately, a series of monocyclic and fused ring heterocyclic precursors were cyclized using the developed methodology. The substrates and cyclized products are summarized in Table 2.

Substrate	Sulfur Heterocycle	Yield (%) [a]
		69
		73
	 (n = 1) (n = 2) (n = 3)	60 69 <5
	 (R,R = Me) (R,R = - $(CH_2)_5$ -	75 71
		78
		76

[a] Yields refer to isolated products

Table 2. Results of Sulfur-Initiated Tandem S_N2-Michael Addition Reactions.

In a tandem process similar to that of the S_N2-Michael reaction, selective acetate cleavage of ethyl (*E*)-ω-acetyloxy-2-hexenoate and heptenoate esters afforded an oxygen anion that could then close on the suitably disposed activated double bond.[56] As Figure 5

illustrates, attack by ethoxide on the acetyloxy carbonyl of **15** generates the tetrahedral intermediate **16**. Collapse of the intermediate gives the alkoxide which can add in Michael fashion to the activated double bond. The design of the substrates are such that, the choice of ester groups dictates selectivity. Only attack at the acetyloxy carbonyl leads to product.

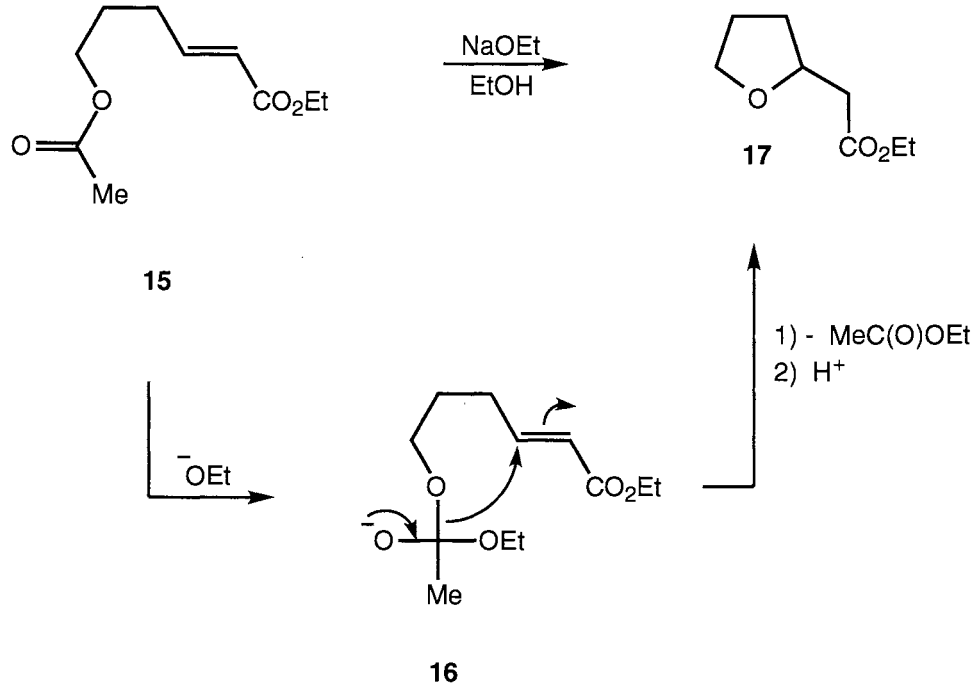
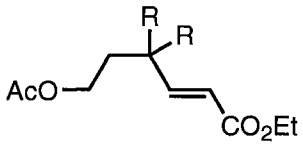
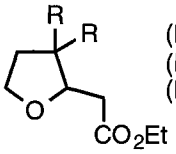
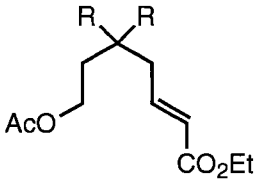
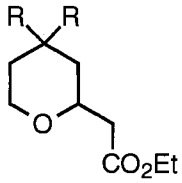
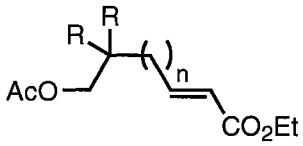
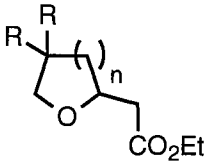
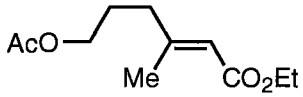
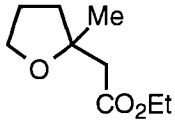


Figure 5. Oxygen Heterocycles via Ester Cleavage-Michael Reaction

The initial success in the cyclization of oxygen heterocycles prompted a series of monocyclic and heterocyclic precurors to be studied. Unlike the nitrogen and sulfur initiated S_N2-Michael tandem reactions, only simple cyclization substrates were investigated. Substrates were identified that could close both five and six-membered rings and the results of the group of cyclizations are summarized in Table 3. Seven-membered rings would not close and gave 1) acetyloxy cleavage and 2) addition of ethoxide to activated double bond.

Substrate	Oxygen Heterocycle	Yield (%) [a]
	 (R,R = H) (R,R = Me) (R,R = - $(CH_2)_5$ -)	74 79 80
	 (R,R = H) (R,R = Me)	84 82
	 (n = 1) (n = 2)	70 85
		90

[a] Yields refer to isolated products

Table 3. Results of Tandem Ester Cleavage-Michael Addition Reactions.

Continued exploration into the possible combinations of anionic processes led to the development of a conjugate addition-Dieckmann cyclization.[57] This particular tandem sequence is different from the others in this chapter in that conjugate addition is used to generate the initial anionic species. Building on the characteristic 1,4-addition of copper-catalyzed Grignard reagents, a subsequent Dieckmann cyclization can be effected by the carbanion generated in the first reaction of the tandem. In Figure 6, the copper-catalyzed

Grignard reagent adds 1,4 to the α,β-unsaturated ester **18**. The resulting enolate **19** cleaves the other ethyl ester to afford the cyclized product **22**.

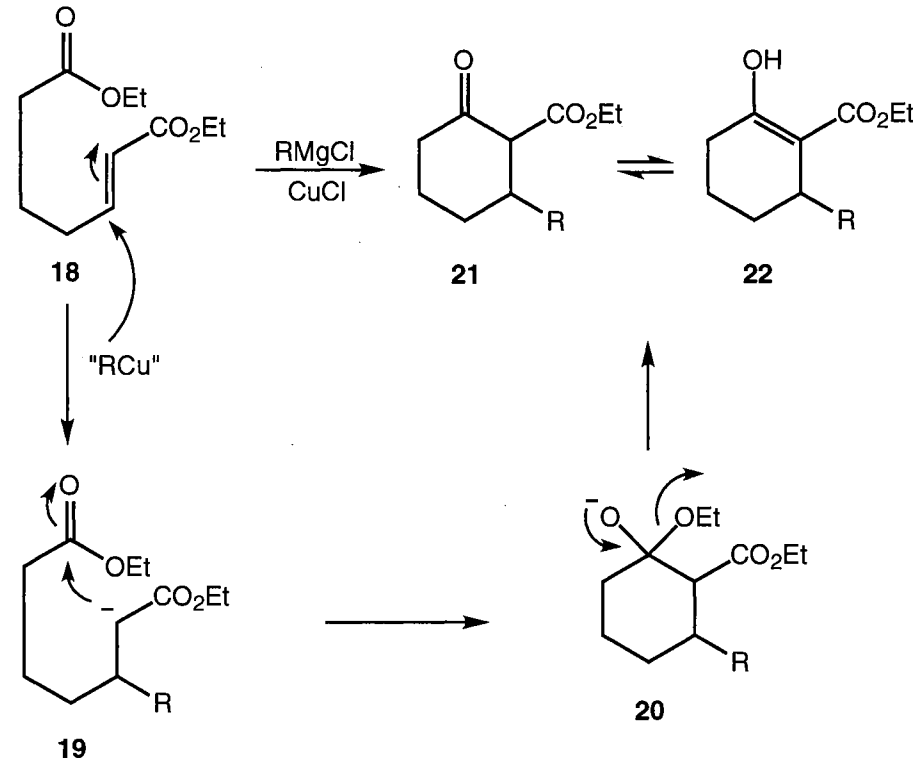


Figure 6. Tandem Conjugate Addition-Dieckmann Cyclization Reaction.

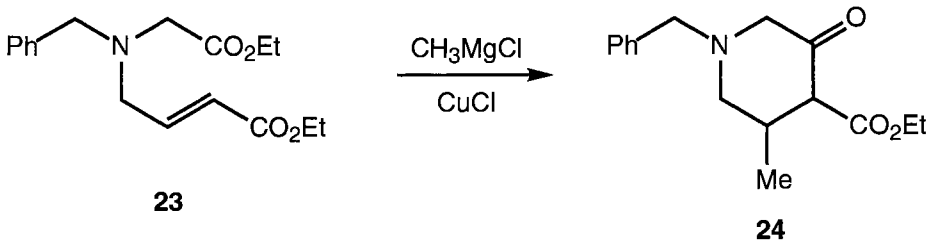


Figure 7. Heterocycles via Conjugate Addition-Dieckmann Cyclization.

By placing a heteroatom into the cyclization substrate, the tandem conjugate addition-Dieckmann cyclization could also be used to synthesize nitrogen heterocycles.[58] Figure 7 shows the copper-catalyzed addition of the methyl Grignard reagent to the *N*-benzyl diester **23**. Subsequent cyclization affords the highly functionalized piperidinone derivative **24**.

In work published by Eilerman and Willis,[59] a new tandem reaction was reported where the anionic species was generated by a dealkoxycarbonylation reaction. The anion could then close on an alkyl halide chain in the same molecule to form a spirocyclic compound. In Figure 8, the β-ketoester **25** was converted to the cyclization substrate **26** in several steps. Subjecting the substrate **26** to the new cyclization conditions afforded the spirocyclic product **27** which was subsequently carried on to spirovetivone **28**.

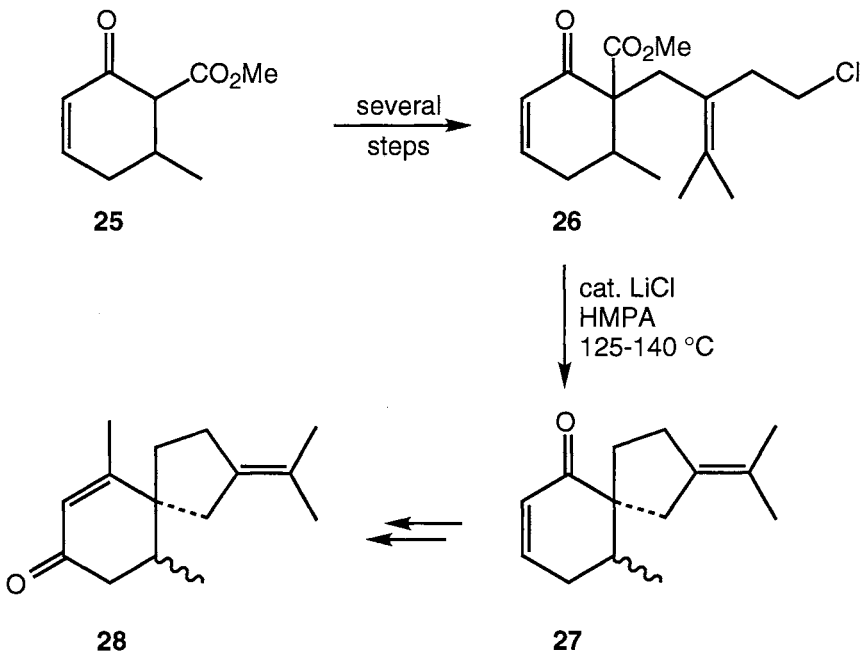
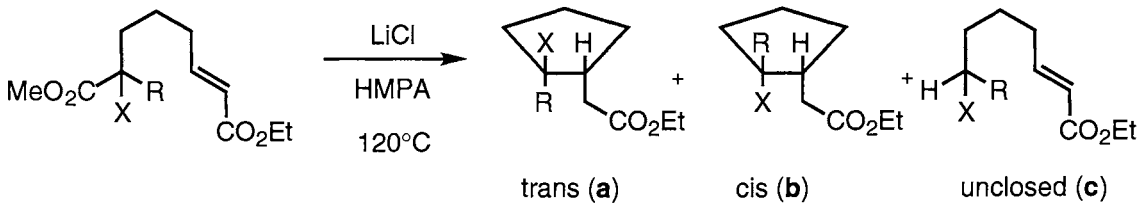


Figure 8. Tandem Dealkoxycarbonylation-S_N2 Reaction.

This first report of using a dealkoxycarbonylation to initiate an anionic tandem reaction led to the study of pairing this process with a Michael reaction. The tandem

dealkoxycarbonylation-Michael addition reaction was first reported in the synthesis of a series of cyclopentane- and cyclohexaneacetic esters.[60] The cyclization substrates contained an activated methyl ester which could be selectively cleaved via S_N2 dealkylation. Subsequent decarboxylation led to a carbanion stabilized by an adjacent electron-withdrawing group. By design, this carbanion could then add in Michael fashion to a strategically placed activated double bond to close a five- or six-membered ring. A general reaction sequence involved treating the cyclization substrates with four equivalents of lithium chloride in hexamethylphosphoramide (HMPA) at 120 °C for 4 h. After acidic workup, the desired ring-closed products were obtained in 45-90% yields with moderate to excellent selectivity. The major isomers possessed a trans relationship with respect to the electron withdrawing group and the acetic ester side chain. Given the potentially hazardous nature of HMPA as a solvent, several other polar aprotic solvents were explored. Among these, 1-methyl-2-pyrrolidinone (NMP), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimindinone (DMPU), and 1,3-dimethyl-2-imidazolidinone (DMEU) were studied as alternatives to HMPA. These experiments met with limited success; the alternative solvents gave better selectivities in some cases but HMPA proved to be a superior solvent for a broader range of examples.



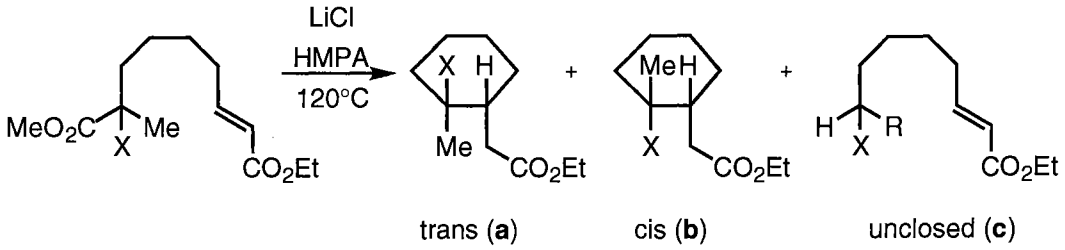
29 (R = Me, X = CO_2Et)
30 (R = Me, X = CO_2Et)
31 (R = Me, X = COMe)
32 (R = Me, X = COMe)
33 (R = Me, X = COPh)
34 (R = Me, X = COPh)
35 (R = Me, X = SO_2Ph)
36 (R = Me, X = SO_2Ph)
37 (R = Me, X = CN)
38 (R = Me, X = CN)

Figure 9. Cyclizations to Yield Cyclopentaneacetic Esters.

A representative cyclization is illustrated in Figure 9, with the results of a series of cyclopentaneacetic ester cyclizations using HMPA summarized in Table 4.

substrate	R	X	product	(**a**):(**b**):(**c**)	yield, (%)
29	Me	CO_2Et	**30**	74 : 26 : 0	64
31	Me	COMe	**32**	93 : 7 : 0	94
33	Me	COPh	**34**	89 : 11 : 0	78
35	Me	SO_2Ph	**36**	99 : 1 : 0	91
37	Me	CN	**38**	77 : 23 : 0	67

Table 4. Synthesis of Cyclopentaneacetic Esters by the Tandem Dealkoxycarbonylation-Michael Addition Reaction.



39 (R = Me, X = CO_2Et)
40 (R = Me, X = CO_2Et)
41 (R = Me, X = COMe)
42 (R = Me, X = COMe)
43 (R = Me, X = COPh)
44 (R = Me, X = COPh)
45 (R = Me, X = SO_2Ph)
46 (R = Me, X = SO_2Ph)
47 (R = Me, X = CN)
48 (R = Me, X = CN)

Figure 10. Representative Tandem Dealkoxycarbonylation-Michael Addition Reaction of Cyclohexaneacetic Esters.

The same cyclization protocol was applied to a series of cyclohexaneacetic esters (Figure 10) with the results compiled in Table 5 below.

substrate	X	product	(**a**):(**b**):(**c**)	yield, (%)
39	CO_2Et	**40**	40 : 10 : 26	[a]
41	COMe	**42**	64 : 12 : 24	55
43	COPh	**44**	74 : 2 : 24	76
45	SO_2Ph	**46**	80 : 5 : 15	82
47	CN	**48**	69 : 15 : 16	45

[a] A complex inseparable mixture was obtained.

Table 5. Synthesis of Cyclohexaneacetic Esters.

The mechanism for nucleophilic dealkylation, decarboxylation, followed by intramolecular alkylative cyclization was first proposed in 1975.[61] In Figure 11, the chloride ion, expected to be a strong nucleophile in polar aprotic solvents, attacks the cyclization substrate **49** to generate a β-ketocarboxylate intermediate. This loses CO_2 to give the ketone-stabilized carbanion **50** which subsequently undergoes an intramolecular alkylation to give the cyclopropane derivative **51**.

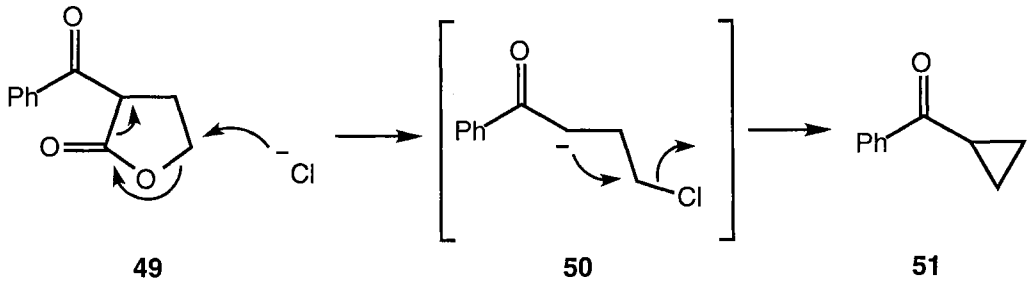


Figure 11. Mechanism of Decarboxylation-Alkylation Reaction.

The proposed mechanism[60] for the tandem dealkoxycarbonylation-Michael reaction (Figure 12) involves selective attack of the nucleophilic chloride ion at the methyl ester of cyclization substrate **52**. This selectivity is explained by the relative reactivities of methyl vs. ethyl substrates in the S_N2 reaction. Examination of rate data indicates that the methyl ester reacts almost thirty times faster than the ethyl ester in the S_N2 reactions.[62] The displacement of the methyl group generates a carboxylate ion. At 120 °C, this decarboxylates to give the stabilized carbanion **54** which adds in Michael fashion to the pendant acrylate ester, affording the cyclized product **55**.

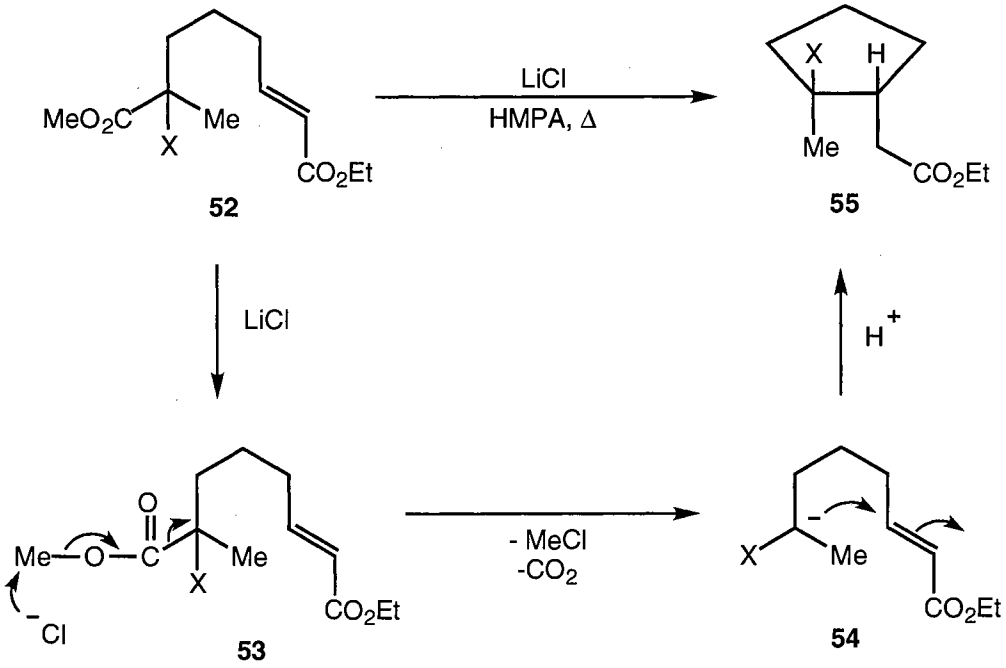


Figure 12. Proposed Mechanism for Tandem Dealkoxycarbonylation-Michael Addition Reaction.

It was found that the reaction worked best for the preparation of cyclopentane derivatives. The cyclization of cyclohexane derivatives resulted in lower yields and higher recovery of uncyclized dealkoxycarbonylated material. The formation of six-membered

rings by this methodology was limited to precursors which generated tertiary carbanions upon decarboxylation; formation of five-membered rings occurred with either secondary or tertiary carbanions. It was suggested that the difference in reactivity was due to electronic, torsional, and entropic factors.[60]

The trans selectivity exhibited by these systems can be explained by considering steric and electronic interactions. In Figure 13, if the functional group X is sterically smaller than methyl,[63] then analysis of the possible transition states leading to ring closure indicated an unfavorable 1,3-interaction in the transition state leading to the trans isomer **57** which is absent in the transition state leading to the cis isomer **56**. Therefore, other non-steric factors must control the stereochemical outcome of the ring closure.

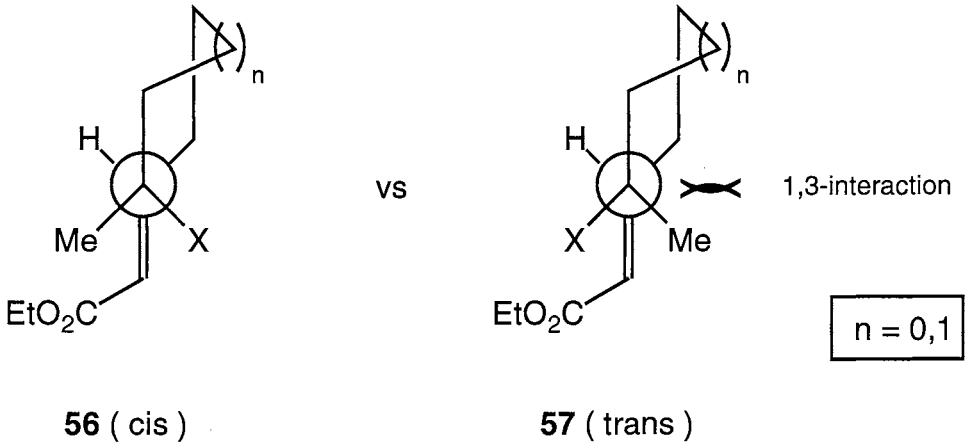


Figure 13. Newman Transition States for Ring Closure.

Calculations suggest[64] that secondary orbital interactions, similar to those invoked to explain the selectivity in Diels-Alder reaction, might play an important role in these types of ring closures. In a compact chair transition state (Figure 14), overlap of the HOMO of the enolate (Michael donor) and the LUMO of the s-cis α,β-unsaturated ester (Michael acceptor) effectively stabilizes the transition state **58.** This stabilization leads to increased selectivity for the trans product **59**.

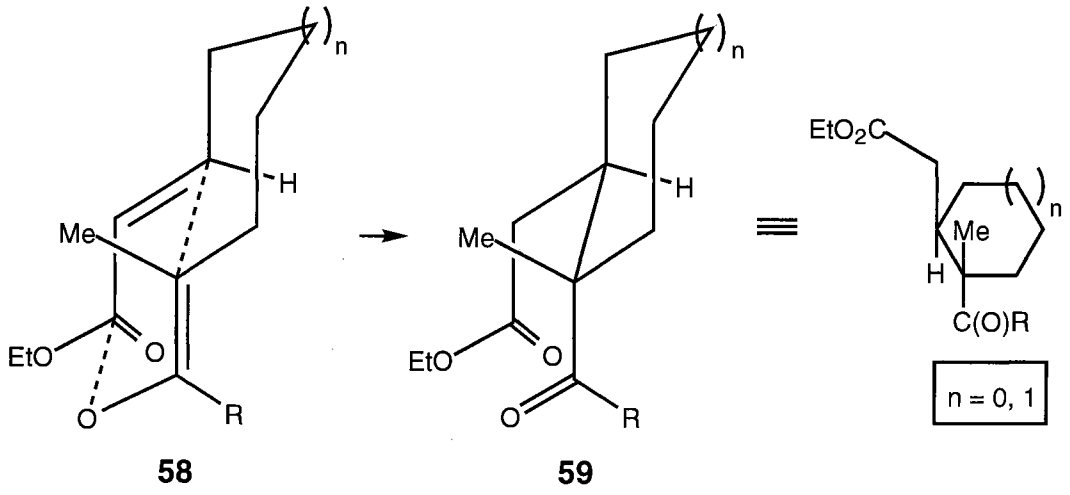


Figure 14. Compact Chair Transition State for Ring Closure.

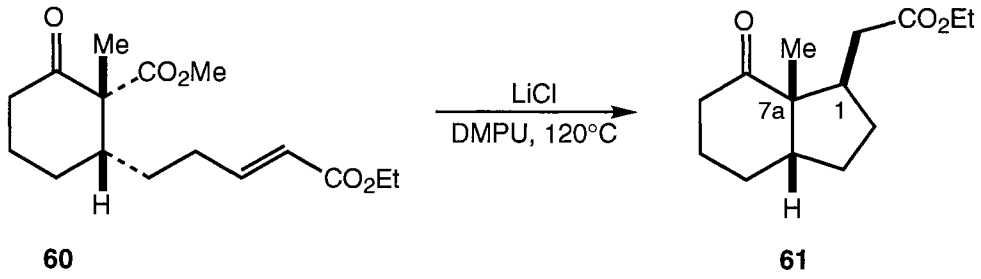


Figure 15. Fused Ring Systems via Tandem Dealkoxycarbonylation-Michael Addition Reaction.

This tandem cyclization has also been used recently in the synthesis of a fused-ring bicyclic compound[65] (Figure 15). Treatment of cyclohexanone diester **60** with lithium chloride in DMPU afforded keto ester **61** whose skeleton is an important ring system in natural product synthesis.[66] The reaction proceeded to give the preferred[66] all-cis arrangement at C(1), C(3a), and C(7a) with high selectivity (>20:1). Using the rationale from the monocyclic systems, the selectivity in this reaction can be similarly explained. As this reaction affords entry into a complex fused ring system, it's broad application to a

number of diverse compounds make this cyclization a potentially useful pathway to several natural products.

Preparation of Oxygen Heterocycles

The tandem dealkoxycarbonylation-Michael addition sequence has recently been applied to the synthesis of highly functionalized tetrahydrofuran and 2*H*-tetrahydropyran derivatives.[67] Examples of this strategy are illustrated in Figure 16 below. The cyclizations followed the same pattern as their carbocyclic counterparts. Chloride ion cleavage of the methyl ester of **62** and **65** generated carboxylate intermediates which then lost CO_2. The resulting stabilized carbanions then added to the activated double bonds of the pendant acrylate esters to afford the tetrahydrofuran derivatives, **63**, and **64,** and the 2*H*-tetrahydropyran derivatives, **66** and **67**, respectively.

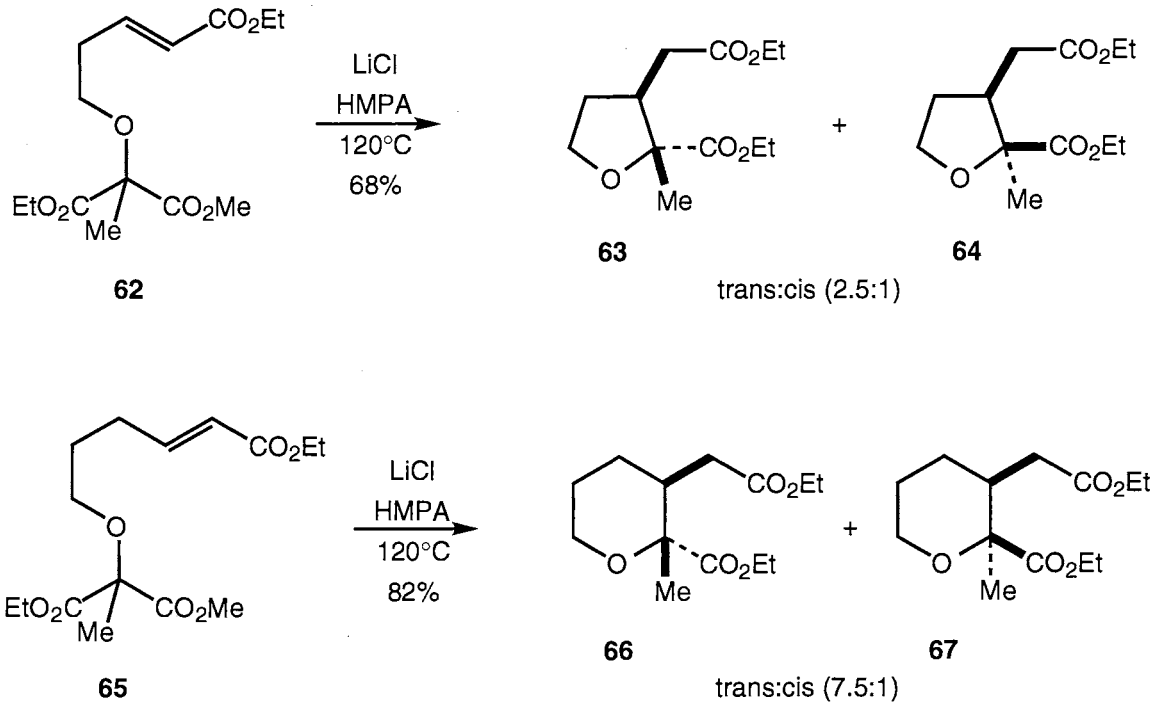


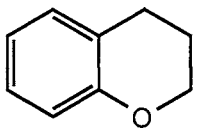
Figure 16. Oxygen Heterocycles by the Tandem Dealkoxycarbonylation-Michael Reaction.

Characterization of the purified products was accomplished by comparison to the ring-closed compounds obtained from the carbocycle series. The results of the oxygen series compared favorably with the carbocycle series in that the functional groups attached to C(2) and C(3) favor the trans conformation.

The same electronic factors that control the previous cyclizations are believed to be working here as well. One characteristic of the oxygen cyclizations was that the selectivity of the six-membered rings was notably better than that of their five-membered counterparts. This was in contrast to the results from the carbocyclic series. The lower selectivity of the five-membered oxygen cyclizations can be attributed to the shorter carbon-oxygen bonds (1.43 Å versus 1.54 Å for the carbon-carbon bonds). The shorter bond length results in a smaller ring which leads to greater strain in achieving the transition state for the five-membered ring closure.[68] The increased strain manifests itself in somewhat less than optimum alignment of the orbitals, leading to less selectivity in the ring-closed product.

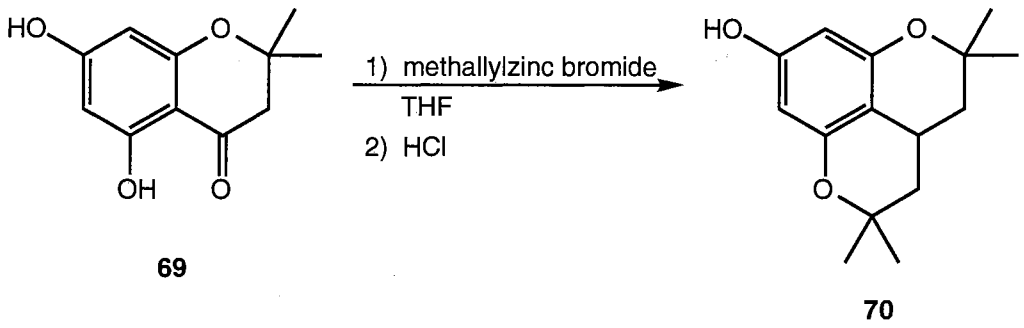
Tandem Dealkoxycarbonylation-Michael Addition Synthesis of 3,4-Dihydro-2*H*-1-benzopyran Derivatives.

The 3,4-dihydro-2*H*-1-benzopyran (chroman) ring system **68** is an important skeletal component of many natural products.[69] The interest in the synthesis of benzopyrans is related to their occurence in many biologically active compounds. These compounds are considered antidepressants, antihypertensive, and hypoglycemic.



68

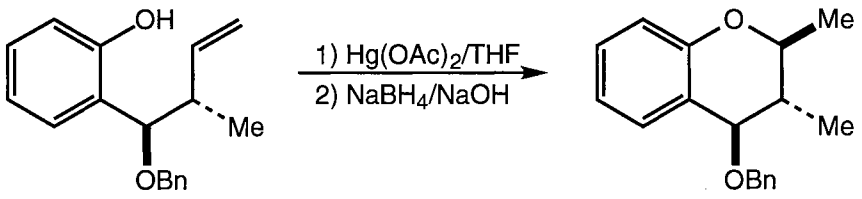
Access to this system has been the subject of several papers. Aukrust and Skattebol, in their recent total synthesis of robustadial A,[70] a naturally occurring chroman derivative, prepared the chroman skeleton via the chromanone **69** which was subsequently reduced to the chroman **70** using methallylzinc bromide to remove the carbonyl (Figure 17).



69 **70**

Figure 17. Synthesis of Chroman Derivative.

In another paper, Baker and Deshpande illustrated access to chiral substituted chroman rings that are related to calophyllum coumarins.[71] In their synthesis[71] (Figure 18), treatment of the appropriate *o*-alkenylphenol **71** with mercuric acetate, followed by $NaBH_4$ reduction, afforded the chiral chroman **72.**



71 **72**

Figure 18. Alternate Synthesis of Chromans.

Several groups have independently reported the use of a tandem dehydration-Diels-Alder sequence in the assembly of the chroman ring systems. In one paper,[72] the synthesis (Figure 19) started with the *o*-quinone methide **74** which was generated by thermal dehydration of *o*-hydroxybenzyl alcohol **73**. This reactive intermediate underwent an intramolecular Diels-Alder cyclization to afford the chroman derivative **75**. The presence of a remote chiral center on the dienophile resulted in stereochemical control in the transition state.

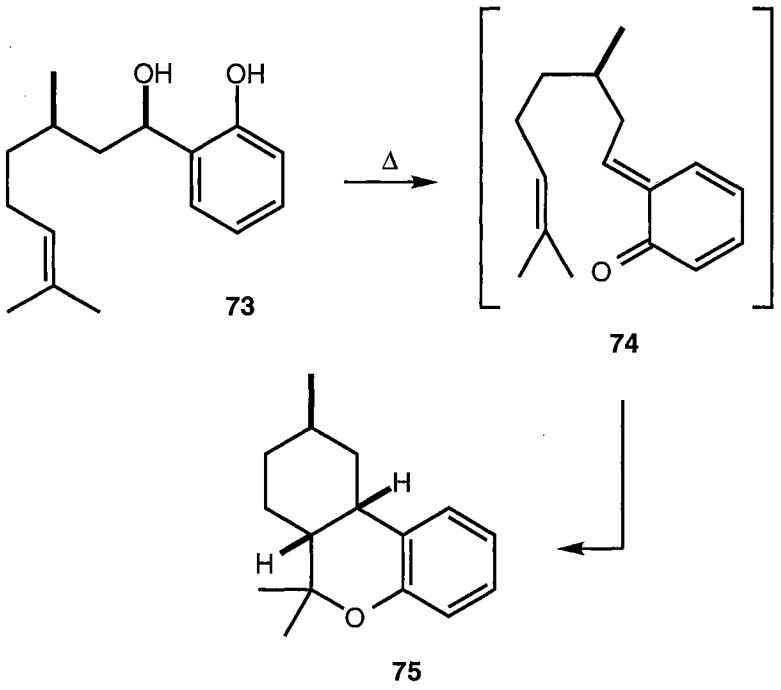


Figure 19. Dehydration-Diels-Alder Synthesis of Chromans.

The current literature contains many examples of routes to these heterocyclic systems. The continued exploration into the applicability of the tandem dealkoxycarbonylation-Michael addition sequence in our lab has demonstrated the ability to access highly functionalized chroman rings.[73] Previous research has shown that methyl esters can be selectively decarboxylated using lithium chloride in polar aprotic solvents to give stabilized carbanions. These anions can then add in Michael fashion to a suitably

disposed pendant acrylate moiety to afford the desired cyclized product. Construction of the cyclization substrates was uneventful and cyclization using optimized reaction conditions afforded the desired products in yields ranging from 50-90%. Figure 20 illustrates the methodology of accessing the chroman system. Starting with cyclization substrates **76** and **78**, previously optimized reaction conditions afforded the cyclized products **77** and **79**. Table 6 summarizes the products, selectivities, and yields obtained.

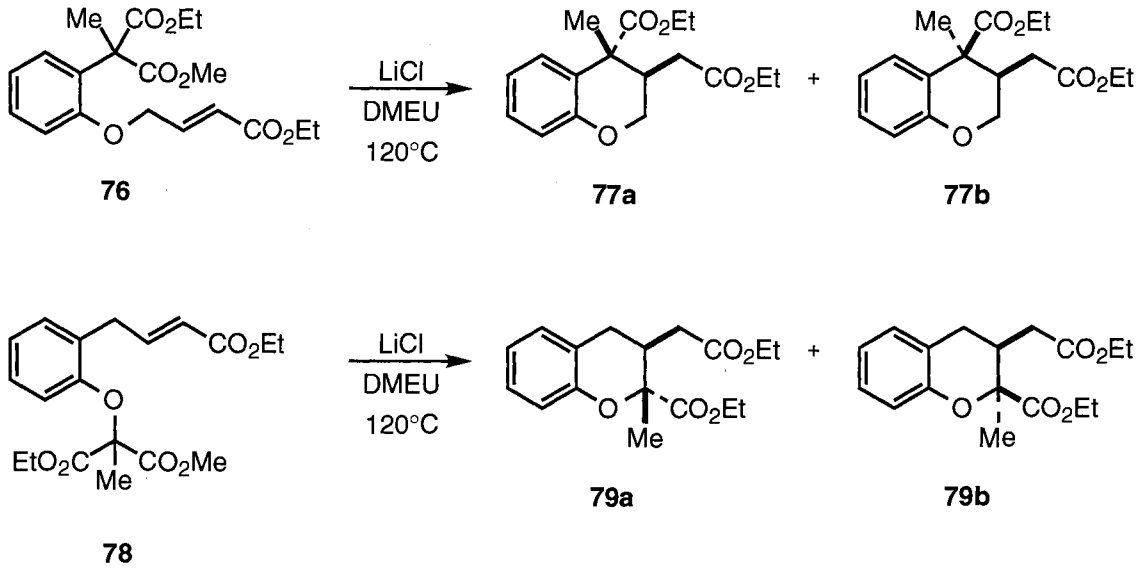


Figure 20. Fused Ring Oxygen Heterocycles via Tandem Dealkoxycarbonylation-Michael Addition Reaction.

Starting Material	Products	a : b[a]	yield, %[b]
76	**77**	**8 : 1**	**89**
78	**79**	**3 : 1**	**54**[c]

[a] Product ratios determined by GC of crude product. [b] Yield refers to isolated purified products. [c] Only trans product was isolated in pure form.

Table 6. Yields and Selectivities in Oxygen Cyclizations.

The mechanism of the reaction is identical to that previously reported.[60] Initial nucleophilic attack occurs selectively at the methyl ester. Dealkylation and subsequent decarboxylation of **76** generates a stabilized carbanion **80** which adds in Michael fashion to the activated double bond of the ethyl acrylate moiety affording an 8:1 ratio of products **77a** and **77b** (Figure 21).

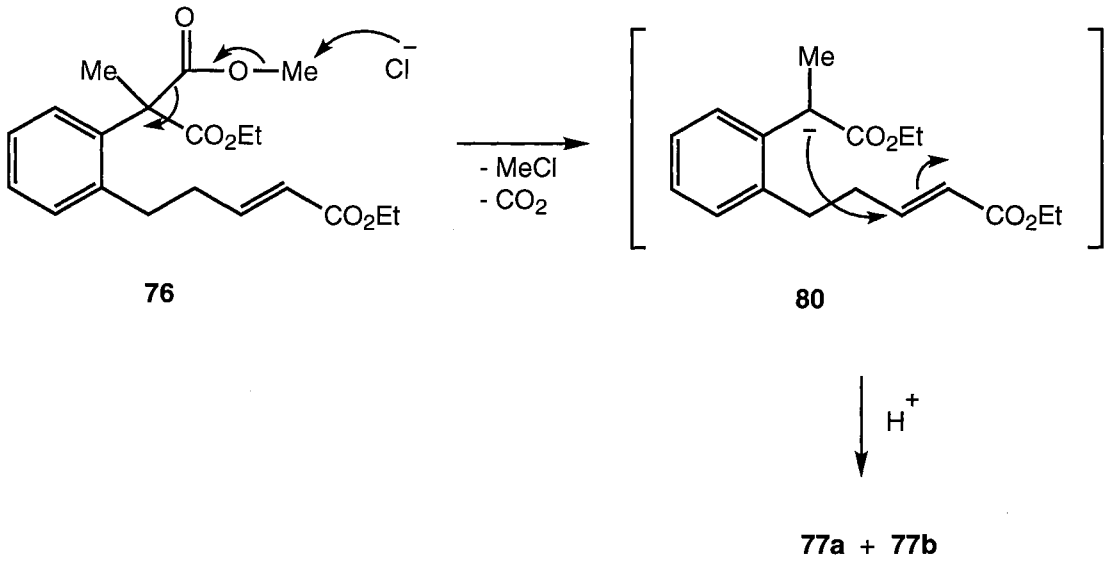


Figure 21. Mechanism of the Dealkoxycarbonylation-Michael Ring Closure.

The structures of the cyclized products were assigned by comparison to those characterized in the simple carbocycle series. In both cases it was determined that the isomer having the ethoxycarbonyl group trans to the acetic ester residue was the major product. The previously reported rationale[63] should apply to chroman cyclizations as well. Using models, analysis of interactions which develop during the ring closures indicates that the steric factors have a minimal effect on the outcome of these cyclizations. Rather, it is believed that electronic factors are the controlling force responsible for the observed selectivity. Calculations reported in the literature[64] suggest that the overlap between the

HOMO of the enolate and LUMO of the s-cis α,β-unsaturated ester **81** stabilizes a chair-like transition state that leads to the trans product **77** (Figure 22).

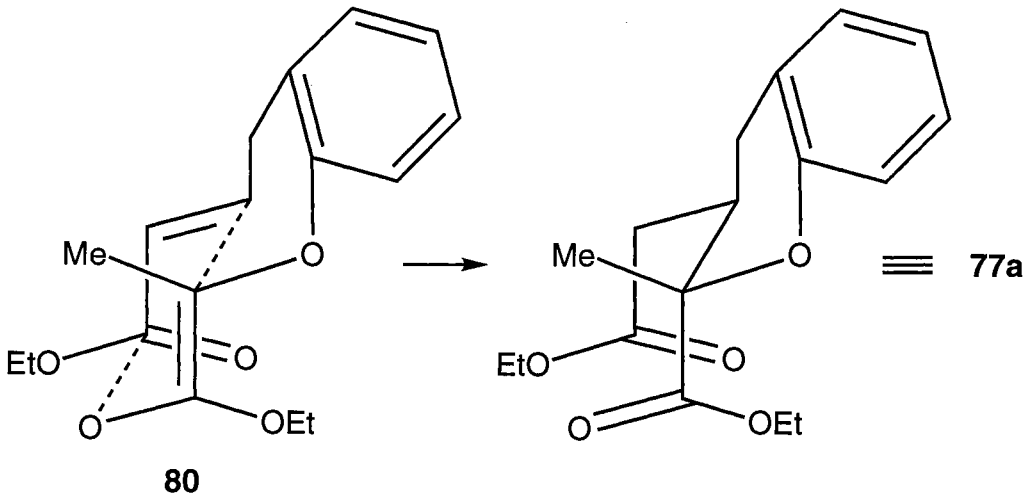


Figure 22. Transition State for the Ring Closure of Chromans.

Conclusion

With the earliest work done in our lab, a concentrated effort has been made to use the Michael addition reaction as part of a tandem sequence. The nature of the Michael addition makes it a good candidate for the second part of a tandem. To that end, candidates for the initiating reaction of the tandem were chosen for their ability to generate an anionic intermediate that can then add in Michael fashion to the designated Michael acceptor. The S_N2-Michael tandem sequence was applicable to nitrogen and sulfur heterocycles. Ester cleavage-Michael addition provided an entry to oxygen heterocycles. The development of the tandem dealkoxycarbonylation-Michael addition reaction has seen the broadening application of tandem processes to an ever increasing number of ring structures in chemistry, both carbocyclic and heterocyclic. Although the general intent of the research is methodological as opposed to target-based synthesis, the results allow entry to many

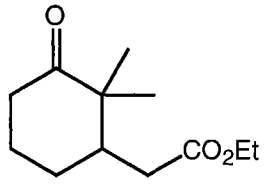
systems that have been investigated as precursors to natural products. The reaction has been applied to both carbocyclic and heterocyclic systems,[60,67,74] polycyclic systems (aliphatic and aromatic),[74] and spirocyclic compounds.[75] The work that has already been accomplished in this area has merely scratched the surface of a far greater body of potential work.

Chapter 4

A Tandem Dealkoxycarbonylation-Michael Addition Route to Highly Functionalized Cyclohexaneacetic Esters.

Introduction

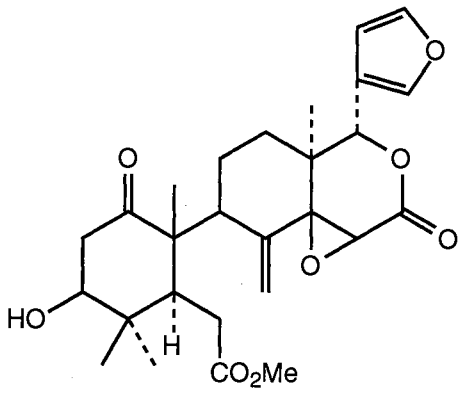
Highly functionalized cyclohexaneacetic esters of the type **1** embody a common skeletal subunit that is found in both the synthetic pathway to natural products as well as the natural products themselves.



1

A synthetic transformation that allows simple and succinct access to these systems gives researchers another tool in their quest for specific compounds. Many of the compounds generated in this study are novel and therefore have no true precedent in the literature. A computer search of the literature recovered many references where the cyclohexaneacetic ester, or a simple derivative, was a key intermediate in the synthesis of a larger molecule. Similarly, several cases were found where the cyclohexaneacetic ester skeletal subunit could be found in the final product.

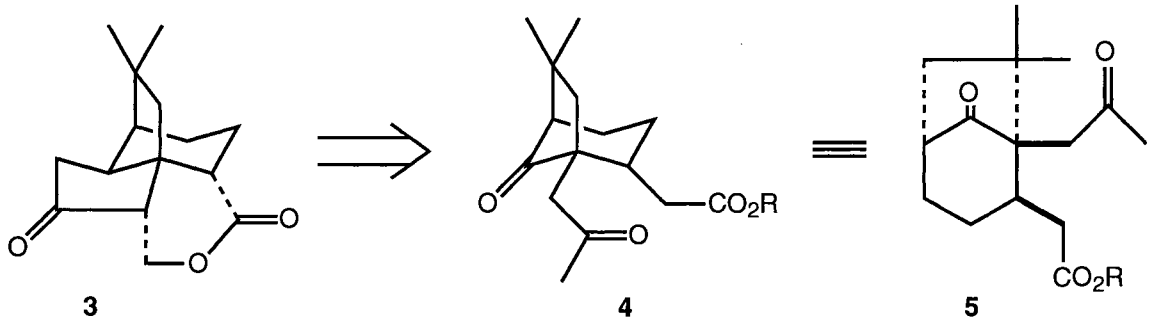
Chakraborty and Das first isolated mahoganin[76] (**2**) in 1968. A non-bitter constituent from *Swietenia mahagoni*, the left-hand ring is a cyclohexaneacetic ester skeletal subunit. (Figure 1)



2

Figure 1. Mahoganin.

Quadrone (**3**) is a sesquiterpene lactone, described as a fungal metabolite from *Aspergillus terreus*,[77] that has been shown to possess antitumor activity. In their total synthesis of (±)-quadrone, Vandewalle and co-workers[78] devised a synthetic pathway that included a functionalized cyclohexaneacetic ester as one their intermediates (Figure 2).



3 **4** **5**

Figure 2. Retrosynthesis of (±)-Quadrone.

In a more recent formal synthesis of quadrone,[79] Little and co-workers developed a pathway that also contained a cyclohexaneacetic ester derivative (Figure 3). Electrochemically initiated cyclization of the nitrile-aldehyde **6** afforded the [3.2.1] framework which, after oxidation with PCC gave the bicyclo[3.2.1]octane derivative **7** containing the cyclohexaneacetic ester subunit.

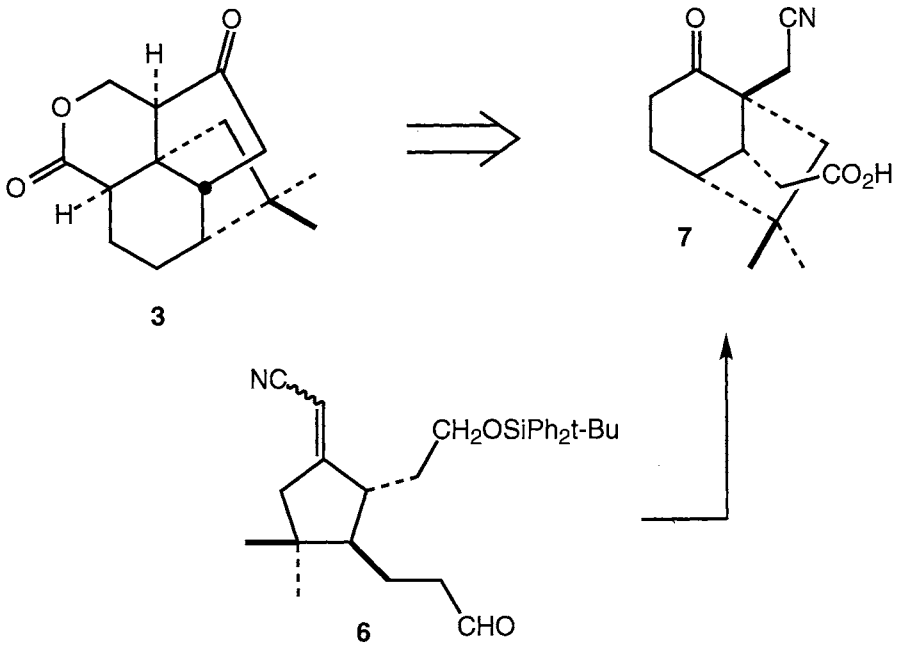


Figure 3. Alternate Synthesis of Quadrone.

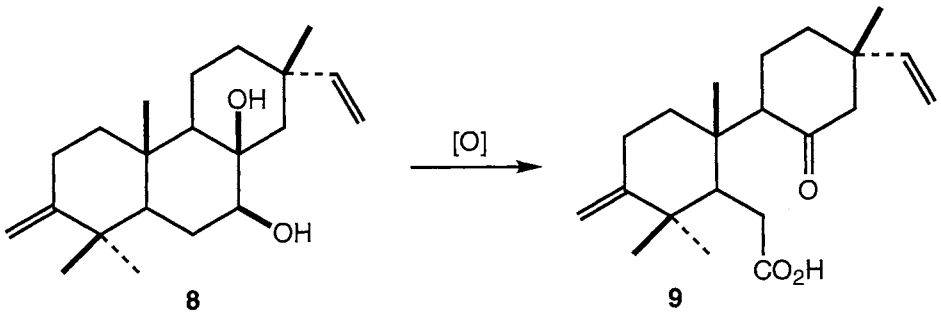


Figure 4. Oxidation of 1,2-Glycols.

In a study of the synthetic utility of the Jones reagent as a tool for oxidative cleavage of 1,2-glycols,[80] Pinto and co-workers reported oxidation products containing cyclohexaneacetic ester derivatives. In Figure 4, the oxidative cleavage of glycol **8** gave ketoacid **9** in 97% yield.

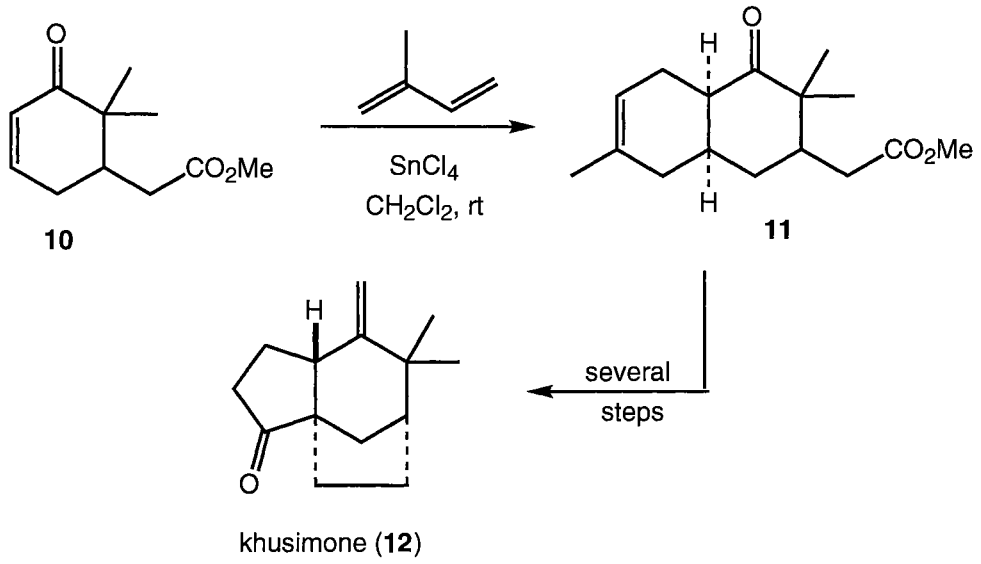


Figure 5. Synthesis of (-)-Khusimone.

Flavors and fragrances constitute a large segment of the useful natural products. Vetiver oil is an important raw material for the fragrance industry. Several of the active (fragrant) components of vetiver oil are zizaene sesquiterpenes. It is thought that these particular sesquiterpenes are responsible for the strong woody and amber-like scents found in many of today's perfumes. Among the zizaene sesquiterpenes, a norsesquiterpene, (-)-khusimone (**12**) was first isolated in 1970.[81] (-)-Khusimone is a minor but olfactively interesting component of vetiver oil which has been shown to have repellent activity against several pests including cockroaches, flies, weevils, and mosquitoes. As important as khusimone is to the perfume industry, it also has an interesting dimethylmethylenetricyclo [6.2.1.$0^{1,5}$]undecane skeleton which has made it a point of synthetic interest.[82]

Khusimone has been obtained by the degradation of natural zizanoic acid and has been synthesized as a racemic mixture by other research groups.[83] Mori and co-workers reported[82] a stereoselective synthesis of (-)-khusimone that started with a cyclohexaneacetic ester derivative **10**. In Figure 5, the tin(IV)chloride mediated Diels-Alder reaction of cyclohexaneacetic ester derivative **10** with isoprene afforded the bicyclo[4.4.0]decane compound **11** which was then carried on to the title compound **12**. In an earlier total synthesis of three sesquiterpenes - (-)-khusimone, (+)-zizanoic acid, and (-)-epizizanoic acid - Chan and Liu[84] also started with cyclohexaneacetic ester derivative **10** (Figure 6). This (-)-khusimone synthesis started with a photoaddition of 1,1-diethoxyethene to generate the bicyclo[4.2.0]octane derivative **13** which was then carried on to (-)-khusimone.

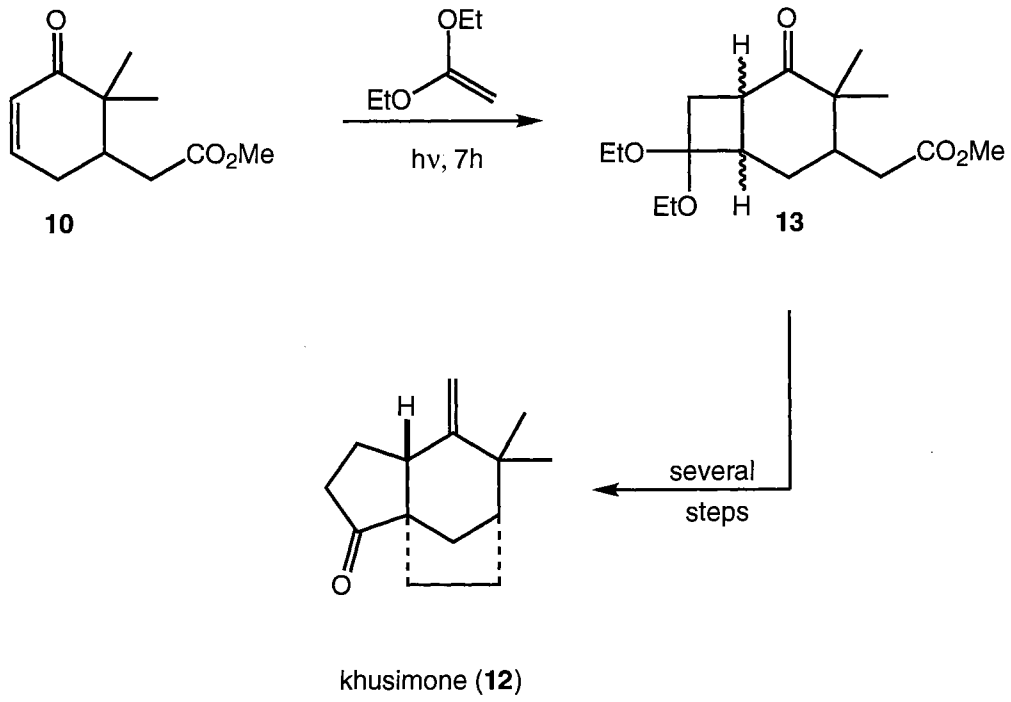


Figure 6. Alternate Synthesis of (-)-Khusimone.

In the same paper, the bicyclo[4.2.0]octane compound derived from the cyclohexaneacetic ester derivative was also used in the synthesis of (+)-khusenic acid **14** and (-)-epizizanoic acid **15** (Figure 7).

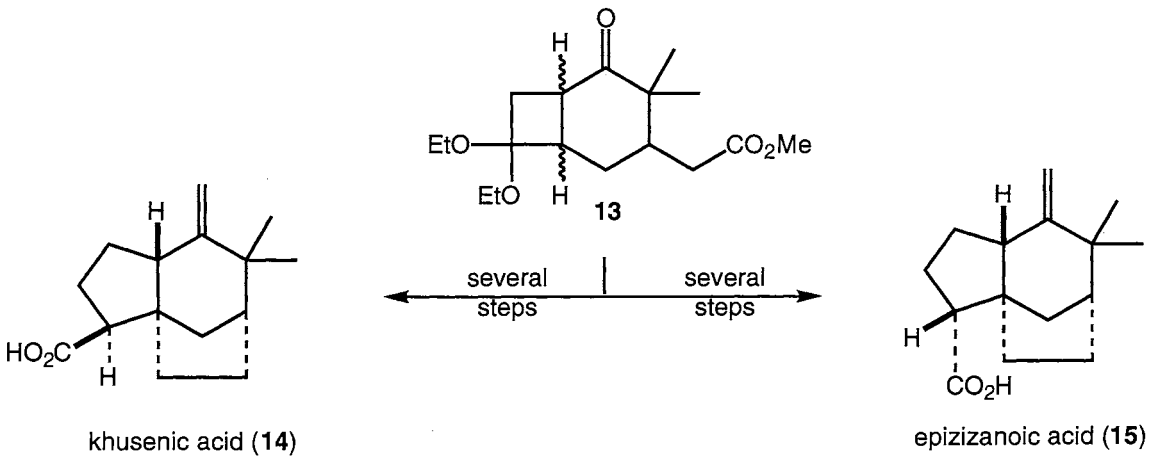


Figure 7. Synthesis of Khusenic Acid and Epizizanoic Acid.

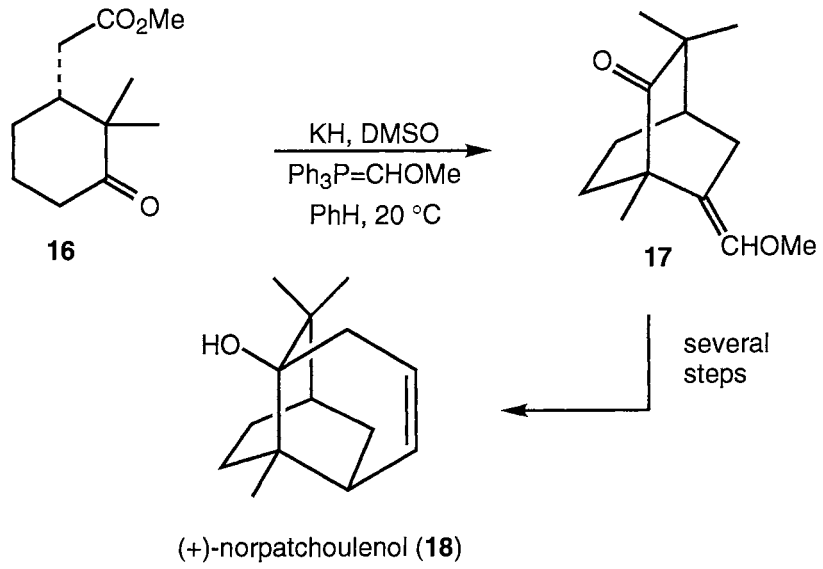


Figure 8. Synthesis of (+)-Norpatchoulenol.

Another staple of the fragrance industry is patchouli oil. In 1973, Teisseire and co-workers[85] reported the isolation of a norsesquiterpene alcohol whose scent was very similar to patchouli oil. The minor constituent was named (+)-norpatchoulenol. Liu and Ralitsch[86] reported a total synthesis of (+)-norpatchoulenol **18** that utilized a cyclohexaneacetic ester derivative as a key intermediate. Starting with **16**, Wittig reaction gave the bicyclo[2.2.2]octane derivative **17** which was then carried on to the title compound **18** (Figure 8).

The limonoid family of compounds possess a bicyclo[3.3.1]nonane skeleton.[87] Many of these natural products are plant extracts. Several examples contain the cyclohexaneacetic ester subunit as part of the skeleton. In a study considering some transformations and interconversions of limonoids, Ekong and co-workers[88] started with mexicanolide (**19**) and, via a series of reactions, converted it to the khivornin derivative **20** (Figure 9). This series of reactions resembles the biogenesis pathway thought to be responsible for the formation of the meliacins and the conversion is postulated as proof that the two classes of compounds are related. The cyclohexaneacetic ester subunit is found in both **19** and **20**.

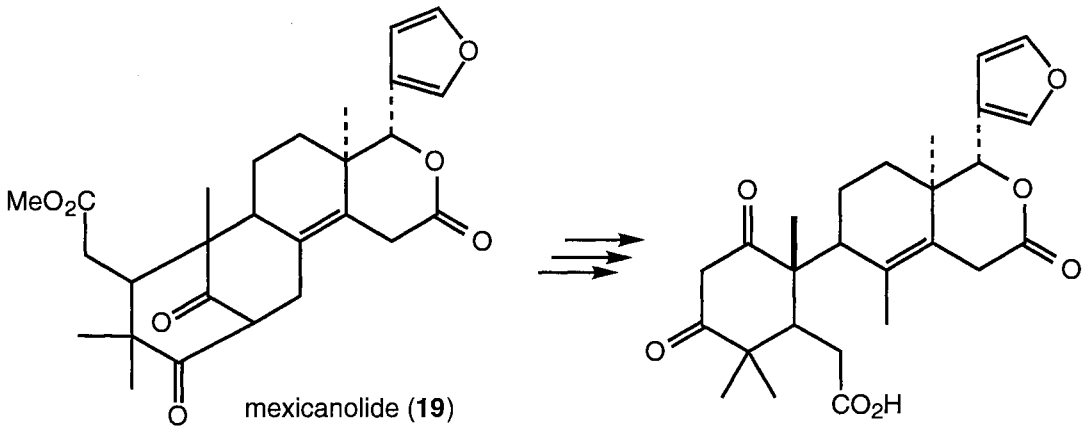


Figure 9. Interconversion of the Meliacins and Gedunin-Khivorins.

In a similar vein, another recent publication studied the synthesis of bicyclo[3.3.1] nonane skeletons.[89] The oxygen-cage compound, 9,9-dimethyl-2-oxabicyclo[3.3.1]-nonane **23** bears resemblance to a series of oxygen-cage compounds known to have anti-viral activity. In Figure 10, the bicyclo[2.2.2]octane derivative **21** is subjected to acid-catalyzed hydrolysis to afford the cyclohexaneacetic acid derivative **22**. Subsequent transformations give the bicyclo[3.3.1]nonane derivative **23**.

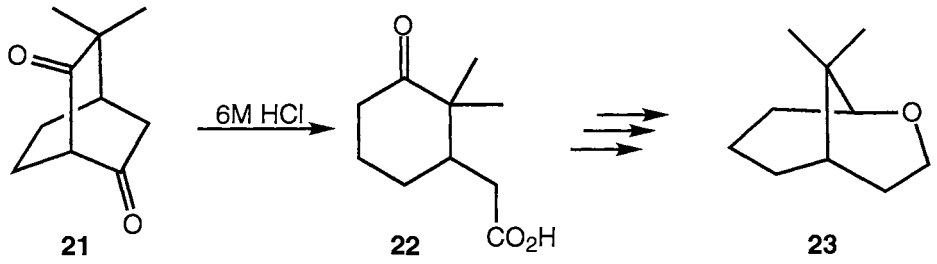


Figure 10. Synthesis of 9,9-Dimethyl-2-oxabicyclo[3.3.1]nonane.

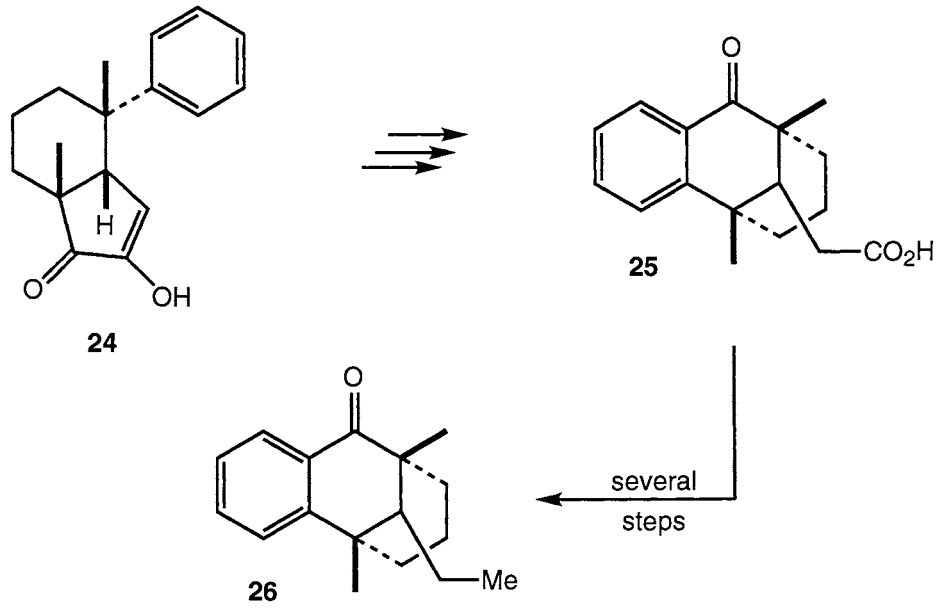


Figure 11. Synthesis of Terpene Derivative.

In an older study, Ireland and co-workers reported the total synthesis of a series of terpenes.[90] Starting with the diosphenol **24**, Figure 11 illustrates the conversion of cyclohexaneacetic ester **25** to cyclohexaneacetic ester **26**.

As can be seen by the previous examples, the cyclohexaneacetic ester subunit is a recurring theme in many natural products. The ability to synthesize such subunits, either separately or as parts of larger molecules, is becoming a requisite tool as target molecules continue to increase in complexity. If such subunits can be introduced via a tandem process, then the overall number of reactions can be reduced. Previous work in this laboratory has illustrated the effectiveness of tandem reactions for accessing these systems. This thesis furthers the applications of tandem processes and synthesizes several novel carbocyclic and spirocyclic products.

Results

A series of cyclization substrates was synthesized that ultimately yielded cyclohexaneacetic ester derivatives. The cyclization reactions completed a three step ring expansion procedure. The key to the ring expansion was a starting material that contained a cyclopentanone moiety. The cyclopentanone unit was converted, via addition, dehydration, and ozonolysis-Wittig sequence, to a substrate that cyclized to give a six-membered ring product. The initial condensation introduced a dialkyl-substituted ester which ultimately became the anionic center in the cyclization reaction. The β-hydroxyester product of the condensation was transformed to the cyclopentene derivative using dehydration conditions. The internal double bond was cleaved by ozonolysis to generate a ketone and an aldehyde, the aldehyde being subsequently converted to the ethyl acrylate functionality by chemoselective Wittig reaction. The ozonolysis-Wittig sequence was an elegant way to introduce two functionalities required in the cyclization substrate. With the general protocol developed, the sequence could be applied to starting materials containing the cyclopentanone moiety.

The synthesis of cyclopenteneacetic ester **29**, is outlined in Figure 12. Treating methyl isobutyrate **27** with LDA in THF at -78 °C generated the anion which was then allowed to react with cyclopentanone.[91] The resulting hydroxy ester **28** was dehydrated, using thionyl chloride in pyridine at 0 °C,[91] to afford the cyclopenteneacetic ester derivative **29**. A similar protocol was employed to access the cyclopenteneacetic ester derivatives **30** and **31**. Starting with methyl cyclopentanecarboxylate and methyl cyclohexanecarboxylate respectively, cyclization substrates **30** and **31** were obtained (Figure 13).

Addition of the anion of methyl isobutyrate with 1- and 2-indanone afforded two isomeric hydroxy esters which, when subjected to $POCl_3$ in pyridine,[92] afforded the two α,α-dimethyl-1*H*-indeneacetic esters. In Figure 14, treatment of methyl isobutyrate with LDA, followed by addition to 1- and 2-indanone gave the hydroxy esters **32** and **33**, respectively. Dehydration of the hydroxy esters was effected using $POCl_3$ in pyridine at 110 °C to afford the 1*H*-indeneacetic esters **34** and **35**.

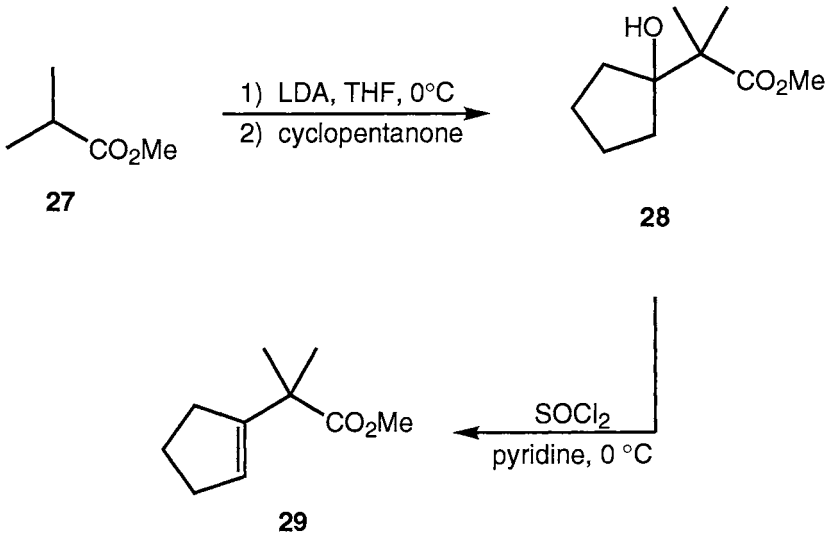
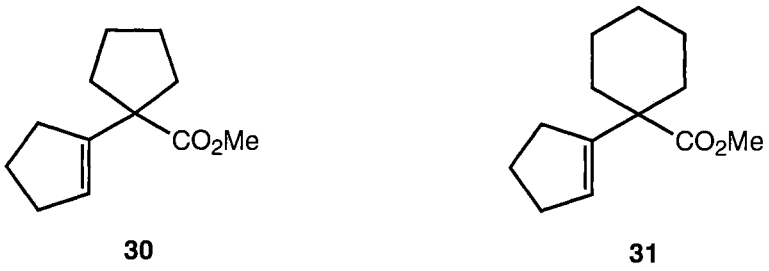


Figure 12. Synthesis of a Dialkyl Cyclopenteneacetic Ester Derivative.



30 31

Figure 13. Spirocyclic Cyclopenteneacetic Ester Derivatives Synthesized.

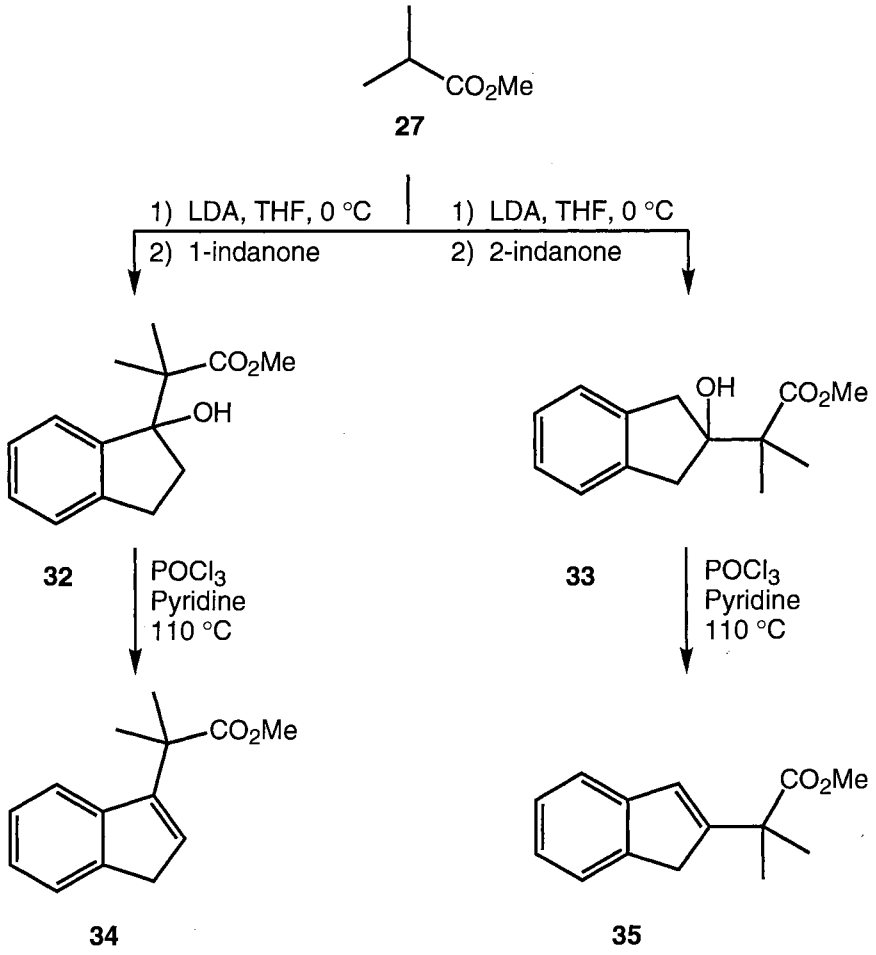


Figure 14. Synthesis of 1*H*-Indeneacetic Ester Derivatives.

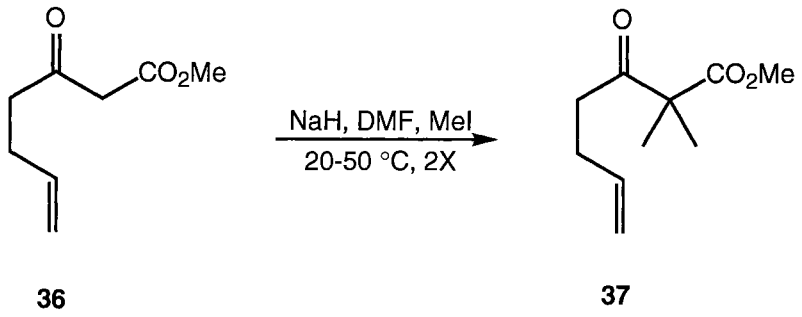


Figure 15. Synthesis of gem-Dimethyl β-Ketoester Precursor.

The cyclization precursor to the five-membered cyclic product required a different synthetic methodology that is outlined in Figure 15. Stepwise dimethylation[93] of the known[94] methyl 3-oxo-6-heptenoate **36** using NaH followed by methyl iodide afforded the gem dimethyl heptenone **37**.

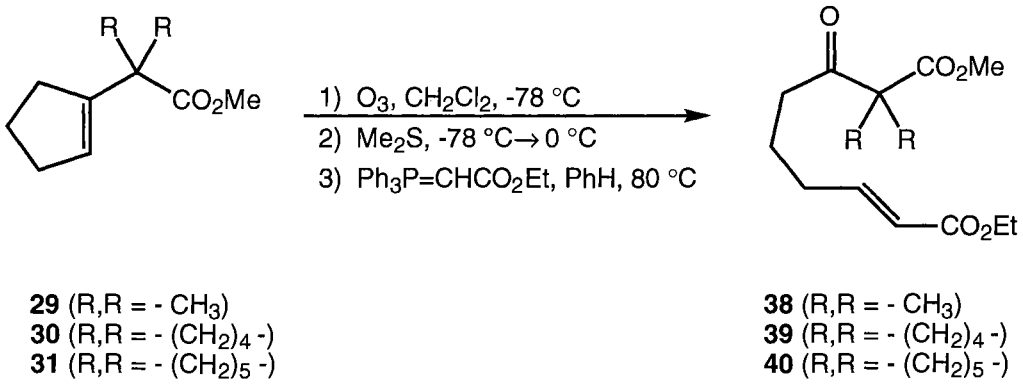


Figure 16. Ozonolysis-Wittig Sequence of Cyclopenteneacetic Ester Derivatives.

Attachment of the requisite acrylate Michael acceptor was accomplished by Wittig olefination of the crude aldehydes derived from ozonolysis, followed by reductive workup, of the unsaturated ester derivatives[60] (Figure 16). The unsaturated ester derivatives (**29**, **30**, and **31**) were subjected to ozonolysis conditions followed by reductive workup using

Me_2S. The resultant crude aldehydes, used without further purification, were refluxed in benzene with ethyl (triphenylphosphoranylidene)acetate to afford the cyclization substrates **38**, **39**, and **40** respectively. The same ozonolysis-Wittig protocol was applied to the 1*H*-indeneacetic ester derivatives (**34** and **35**) to afford the cyclization substrates **41a** and **42**.

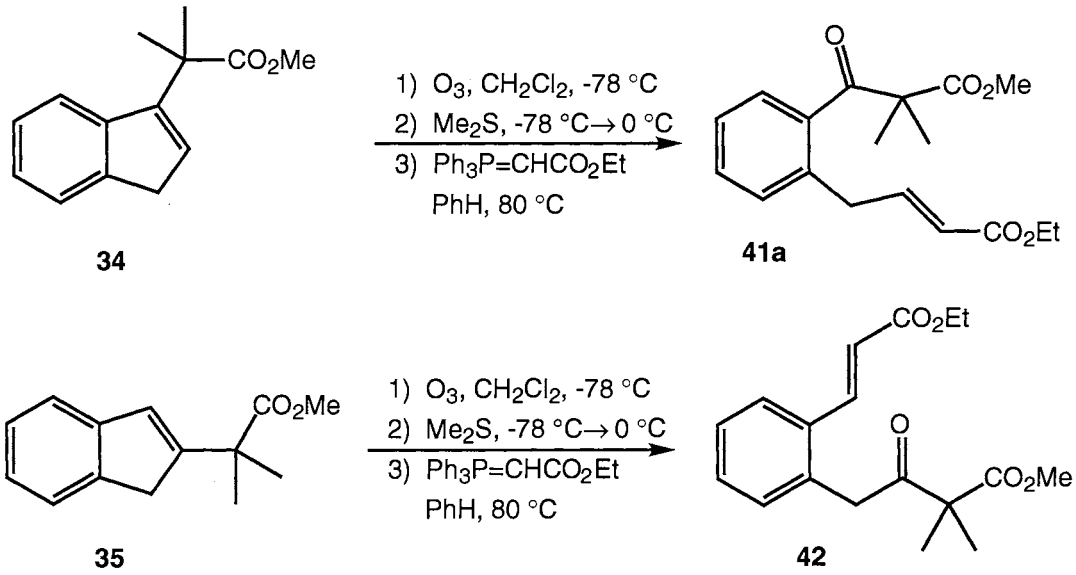


Figure 17. Ozonolysis-Wittig Reaction of 1*H*-Indeneacetic Ester Derivatives.

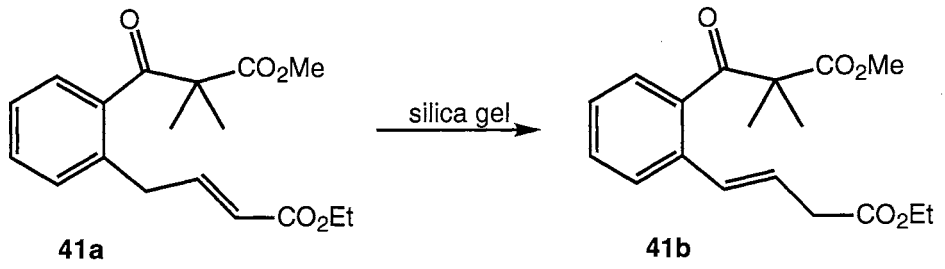
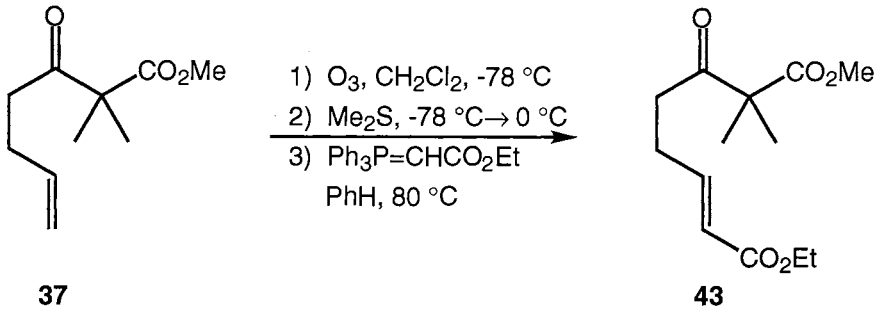


Figure 18. Acid-Promoted Isomerization of **41a**.

The overall yield of **41a** was lowered due to an acid-promoted process that isomerized the double bond of the acrylate into conjugation with the aromatic ring. The isomerization is

thought to have occurred during purification on silica gel (Figure 18), generating **41b** as the major product. In Figure 19, the same ozonolysis-Wittig sequence was used to convert the alkene derivative **37** to the cyclization substrate **43**. The overall yields of the cyclization substrates are listed below in Table 1.



37 **43**

Figure 19. Ozonolysis-Wittig Reaction of Alkene Derivative.

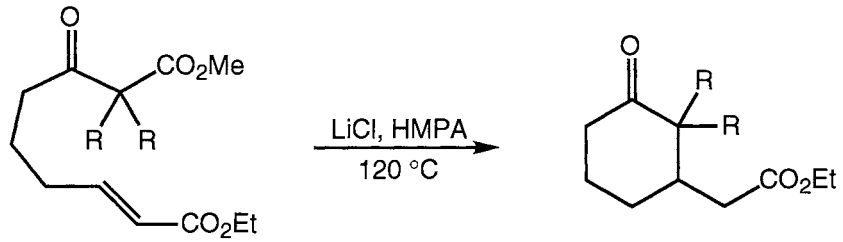
Substrate	Yield, (%)[a]
38 (R, R = - CH_3)	48
39 (R, R = - $(CH_2)_4$ -)	56
40 (R, R = - $(CH_2)_5$ -)	42
42	65
41a[b]	15
43	48

[a] Yields refer to isolated purified products. [b] Product accompanied by 52% of **41b**.

Table 1. Yields of Cyclization Substrates.

Results of Tandem Dealkoxycarbonylation-Michael Addition Reactions.

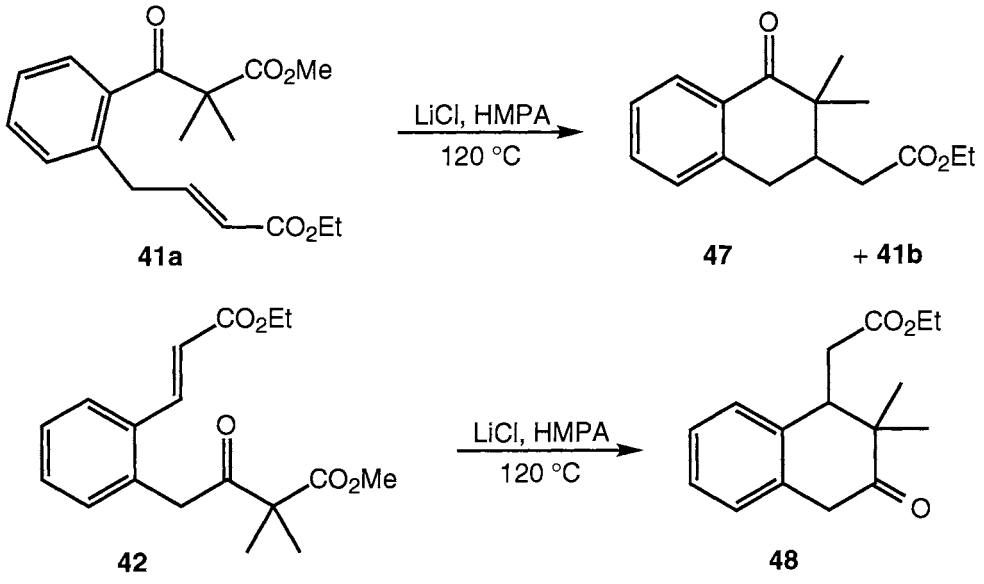
With the cyclization substrates in hand, the precursors were subjected to optimized reactions conditions. Heating the keto diester with four equivalents of LiCl in dry HMPA at 120 °C (± 5 °C) for four hours afforded the desired cyclized products **44-48** in yields ranging from 40-50%. Optimum yields were achieved using reaction scales of 1-5 mmol and substrate concentrations of ≤ 0.1 M (Figure 20).



38 (R,R = - CH_3)
39 (R,R = - $(CH_2)_4$ -)
40 (R,R = - $(CH_2)_5$ -)

44 (R,R = - CH_3)
45 (R,R = - $(CH_2)_4$ -)
46 (R,R = - $(CH_2)_5$ -)

Figure 20. Synthesis of Cyclohexaneacetic Esters.



41a **47** + **41b**

42 **48**

Figure 21. Synthesis of Indeneacetic Esters.

Figure 21 illustrates the application of the cyclization protocol to the 1*H*-indeneacetic ester cyclization substrates **41a** and **42** giving the fused ring aromatic products **47** and **48**.

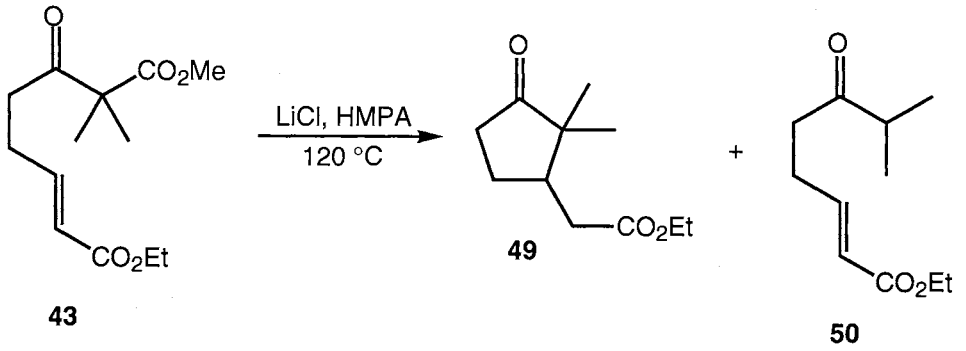


Figure 22. Synthesis of Cyclopentaneacetic Ester.

Substrate	Product	Yield, (%) [a]
38	**44**	74
39	**45**	63
40	**46**	60
42	**48**	63
41a	**47**[b]	46
43	**49**	24[c]

[a] Yields refer to isolated purified products. [b] Product accompanied by 22% of **41b**. [c] Product accompanied by 52% of **50**.

Table 2. Yields of Cyclization Products

An unexpected result was encountered when substrate **43** was subjected to cyclization conditions, yielding 24% of the cyclized product **49** as well as 52% of the dealkoxycarbonylated uncyclized product **50** (Figure 22). The cyclohexaneacetic esters

form by a favorable 6-[*enolendo*]-*exo-trig* ring closure. The transition state for the cyclopentaneacetic ester involves a 5-[*enolendo*]-*exo-trig* ring closure which is disfavored. The difficulty in closure arises from stereoelectronic effects where the planarity of the enolate restricts the reacting centers from obtaining the optimum geometry for cyclization. The overall yields of the cyclization reaction are listed in the Table 2.

In summary, a ring expansion strategy utilizing the tandem dealkoxycarbonylation-Michael addition reaction was developed and optimized. The three-step method is simple to perform and furnishes the final products in good overall yield. The procedure is novel in providing hindered 2,2-dialkyl-3-oxocyclohexaneacetic esters which would be difficult to obtain by conventional means. It has also been demonstrated that the disfavored 5-[*enolendo*]-*exo-trig* cyclization reaction proceeds for the preparation of five-membered rings though yields are not synthetically useful.

Experimental

Solvents were purified in the following manner: DMF and HMPA were stored under nitrogen over 4-Å molecular sieves, THF was distilled from $LiAlH_4$, and diisopropylamine was distilled from CaH_2. Other reagents were used as received. All reactions were run under dry N_2. Unless otherwise indicated, the saturated NH_4Cl, saturated $NaHCO_3$, 5% $Na_2S_2O_3$, saturated NaCl, and 0.5-1.0 *M* HCl used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) visualized using UV light, phosphomolybdic acid, or I_2 vapor or (2) capillary GC with FI detection (SE-30 column, 6-m x 0.25-mm i.d., 0.25-μm film thickness) programmed between 50-300°C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates[95] (Analtech), (2) flash chromatography[96] on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sylvania no. 2282), (3) flash vacuum chromatography[97] on silica gel (60-200 mesh). Band elution, where

appropriate, was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra are referenced to polystyrene. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively, and are referenced to internal $(CH_3)_4Si$. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV. Elemental analyses are ± 0.3%.

Methyl α,α-dimethyl-1-cyclopenteneacetate (29). This compound was prepared in 82% yield according to the procedure of Engel.[91] This same procedure was adapted for the preparation of methyl 1-(1-cyclopentenyl)cyclopentanecarboxylate (**30**), methyl 1-(1-cyclopentenyl)cyclohexanecarboxylate (**31**), methyl 2,3-dihydro-2-hydroxy-α,α-dimethyl-1*H*-indene-2-acetate (**33**), and methyl (±)-2,3-dihydro-1-hydroxy-α,α-dimethyl-1*H*-indene-1-acetate (**32**). The spectral data were as follows:

Methyl 1-(1-Cyclopentenyl)cyclopentanecarboxylate (30): 7.53 g (38.8 mmol, 74%); IR (thin film) 1730, 1640 cm^{-1}; ^{1}H NMR δ 5.50 (quintet, 1 H, J = 2.1 Hz), 3.67 (s, 3 H), 2.33 (m, 2 H), 2.26 (m, 2 H), 2.22 (m, 2 H), 1.86 (quintet, 2 H, J = 7.5 Hz), 1.77 (m, 2 H), 1.63 (m, 4 H); ^{13}C NMR δ 176.5, 145.4, 124.6, 56.4, 52.0, 34.8, 32.8, 32.3, 24.0, 23.5; HRMS *m/e* for $C_{12}H_{18}O_2$: calcd 194.1307. Found: 194.1302.

Methyl 1-(1-Cyclopentenyl)cyclohexanecarboxylate (31): 6.97 g (33.5 mmol, 70%); IR (thin film) 1731, 1630 cm^{-1}; ^{1}H NMR δ 5.51 (quintet, 1 H, J = 2.1 Hz), 3.67 (s, 3 H), 2.31 (m, 2 H), 2.26 (m, 2 H), 2.17 (d, 2 H, J = 13.3 Hz), 1.82 (quintet, 2 H, J = 7.4 Hz), 1.62-1.47 (complex, 5 H), 1.40-1.21 (complex, 3 H); ^{13}C NMR δ 175.5, 146.5, 125.1, 51.7, 49.4, 33.2, 32.4, 31.8, 25.7, 23.4, 23.1; HRMS *m/e* for $C_{13}H_{20}O_2$: calcd 208.1463. Found: 208.1458.

Methyl (±)-2,3-Dihydro-1-hydroxy-α,α-dimethyl-1*H*-indene-1-acetate (32): 13.8 g (59.1 mmol, 78%); IR (thin film) 3480, 1725, 1705, 1390, 1370, 763 cm^{-1}; ^{1}H NMR δ 7.26-7.16 (complex, 4 H), 4.77 (s, 1 H), 3.77 (s, 3 H), 2.99 (m, 1 H), 2.82 (m, 1 H), 2.42 (m, 1 H), 2.17 (m, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR δ

179.4, 144.4, 144.0, 128.3, 126.4, 124.1, 86.9, 52.3, 50.2, 37.7, 30.7, 21.4, 20.8; HRMS *m/e* for $C_{14}H_{18}O_3$: calcd 234.1256. Found: 234.1257.

Methyl 2,3-Dihydro-2-hydroxy-α,α-dimethyl-1*H*-indene-2-acetate (33): 9.22 g (39.4 mmol, 52%); IR (thin film) 3510, 1730, 1390, 1370, 741 cm^{-1}; ^1H NMR δ 7.20-7.14 (complex, 4 H), 3.74 (s, 3 H), 3.38 (s, 1 H), 3.27 (d, 1 H, *J* = 16.7 Hz), 2.92 (d, 1 H, *J* = 16.7 Hz), 1.32 (s, 6 H); ^{13}C NMR δ 178.4, 140.9, 126.5, 124.7, 85.2, 52.1, 48.9, 43.2, 22.0; HRMS *m/e* for $C_{14}H_{18}O_3$: calcd 234.1256. Found: 234.1252.

Representative Procedure for the Preparation of 1*H*-Indeneacetate Esters: Methyl α,α-Dimethyl-1*H*-indene-2-acetate (35). The general procedure of Allen[93] was used. To a stirred 0°C solution of 8.5 g (36.3 mmol) of **33** in 75 mL of pyridine was added 11.1 g (6.8 mL, 72.6 mmol) of phosphorous oxychloride dropwise during 30 min. The mixture was heated to reflux for 2 h, cooled to rt, poured onto 250 g of crushed ice, and ether extracted (3 x 100 mL). The combined ether extracts were washed with 1 *M* HCl (3 x 150 mL), H_2O, $NaHCO_3$, and NaCl, then dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography on a 30 cm x 2 cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the major band gave 6.48 g (30.0 mmol, 83%) of **15** as a clear yellow oil which crystallized to a yellow solid, mp 27-28 °C; IR (thin film) 1738, 1610, 1388, 1369, 752 cm^{-1}; ^1H NMR δ 7.39 (d, 1 H, *J* = 7.4 Hz), 7.31 (d, 1 H, *J* = 7.4 Hz), 7.25 (m, 1 H), 7.14 (m, 1 H), 6.68 (s, 1 H), 3.67 (s, 3 H), 3.41 (s, 2 H), 1.53 (s, 6 H); ^{13}C NMR δ 176.5, 152.3, 144.5, 143.1, 126.7, 126.3, 123.5, 120.7, 52.2, 44.7, 38.7, 25.7; HRMS *m/e* for $C_{14}H_{16}O_2$: calcd 216.1150. Found: 216.1145.

Methyl α,α-Dimethyl-1*H*-indene-3-acetate (34): 5.58 g (25.8 mmol, 78%), mp 35-36 °C; IR (thin film) 1740, 1608, 1385, 1365, 768 cm^{-1}; ^1H NMR δ 7.45 (d, 1 H, *J* = 6.9 Hz), 7.27-7.20 (complex, 2 H), 7.18 (t, 1 H, *J* = 7.2 Hz), 6.37 (quintet, 1 H, *J* = 2.1 Hz), 3.62 (s, 3 H), 3.35 (d, 2 H, *J* = 2.1 Hz), 1.59 (s, 6 H); ^{13}C NMR δ

177.2, 147.6, 144.8, 143.3, 127.6, 126.0, 124.4, 123.9, 120.2, 52.2, 43.3, 37.3, 25.3; HRMS *m/e* for $C_{14}H_{16}O_2$: calcd 216.1150. Found: 216.1152.

Methyl 2,2-Dimethyl-3-oxo-6-heptenoate (37). This compound was prepared by treating 7.67 g (49.2 mmol) of methyl 3-oxo-6-heptenoate[93] twice with 1 equivalent of NaH and 1.1 equivalent of MeI according to the procedure described previously.[94] The crude product was chromatographed on a silica gel column eluted with increasing concentrations of ether in hexanes to give 7.52 g (40.9 mmol, 83%) of **37** as a light yellow oil. IR (thin film) 3085, 1752, 1725, 1648, 1395, 1375, 1000, 920 cm^{-1}; ^1H NMR δ 5.78 (ddt, 1 H, *J* = 17.0, 10.3, 6.7 Hz), 5.03 (d, 1 H, *J* = 17.0 Hz), 4.98 (d, 1 H, *J* = 10.3 Hz), 3.73 (s, 3 H), 2.55 (t, 2 H, *J* = 7.1 Hz), 2.32 (m, 2 H), 1.37 (s, 6 H); ^{13}C NMR δ 207.1, 174.1, 137.0, 115.3, 55.5, 52.4, 37.2, 27.8, 21.9; HRMS *m/e* for $C_{10}H_{16}O_3$: calcd 184.1099. Found: 184.1104.

Representative Ozonolysis-Wittig Procedure: 1-Ethyl Methyl (*E*)-8,8-Dimethyl-7-oxo-2-nonenedioate (38). A 300 mL CH_2Cl_2 solution of 13.1 g (71 mmol) of **29** was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 8.83 g (10.4 mL, 142 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated in vacuo. To the resulting yellow oil was added 150 mL of benzene and 35.5 g (102 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was refluxed for 12 h, then cooled and concentrated to afford a tan semisolid mass. The residue was loaded onto a 10 cm x 10 cm plug of silica gel in a sintered glass frit, and 1 L of 15% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude diester as a light yellow oil. The crude product was flash chromatographed on a silica gel column eluted with increasing concentrations of ether in hexanes to give 11.2 g (41.5 mmol, 58%) of **38** as a light yellow oil. IR (thin film) 1750, 1730, 1718, 1660, 1390, 1372 cm^{-1}; ^1H NMR δ 6.91 (dt, 1 H, *J* = 15.6, 6.9 Hz), 5.81 (d, 1 H, *J* = 15.6 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz), 3.72 (s, 3 H), 2.48 (t, 2 H, *J* = 7.2 Hz), 2.19 (m, 2 H), 1.77 (quintet, 2 H, *J* =

7.2 Hz), 1.37 (s, 6 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 207.3, 174.1, 166.5, 148.0, 122.0, 60.2, 55.5, 52.5, 36.9, 31.2, 22.0 (3), 14.2; HRMS *m/e* for $C_{14}H_{22}O_5$: calcd 270.1467. Found: 270.1469.

Other compounds prepared using this procedure, though on different scales, are given below. The compounds were purified by silica gel column chromatography eluted with increasing concentrations of anhydrous diethyl ether in hexanes.

Ethyl (*E*)-7-(1-Methoxycarbonylcyclopentyl)-7-oxo-2-heptenoate (39): 5.78 g (19.5 mmol, 75%); IR (thin film) 1744, 1723, 1668 cm^{-1}; ^{1}H NMR δ 6.90 (dt, 1 H, J = 15.6, 6.9 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.72 (s, 3 H), 2.45 (t, 2 H, J = 7.1 Hz), 2.19 (m, 2 H), 2.10 (m, 4 H), 1.77 (m, 2 H), 1.64 (m, 4 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 205.5, 173.9, 166.5, 148.0, 121.9, 66.6, 60.2, 52.5, 37.7, 33.1, 31.2, 25.5, 22.2, 14.2; HRMS *m/e* for $C_{16}H_{24}O_5$: calcd 296.1624. Found: 296.1617.

Ethyl (*E*)-7-(1-Methoxycarbonylcyclohexyl)-7-oxo-2-heptenoate (40): 5.80 g (18.7 mmol, 60%); IR (thin film) 1740, 1729, 1710, 1668 cm^{-1}; ^{1}H NMR δ 6.90 (dt, 1 H, J = 15.6, 6.9 Hz), 5.81 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.72 (s, 3 H), 2.47 (t, 2 H, J = 7.1 Hz), 2.19 (m, 2 H), 2.08 (m, 2 H), 1.74 (m, 4 H), 1.58-1.27 (complex, 6 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 206.8, 172.8, 166.4, 147.9, 121.9, 61.1, 60.1, 52.2, 36.8, 31.1, 30.6, 25.1, 22.7, 21.8, 14.2; HRMS *m/e* for $C_{17}H_{26}O_5$: calcd 310.1780. Found: 310.1773.

Methyl (*E*)-3-(2-(3-Ethoxycarbonyl-1-propenyl) phenyl)-2,2-dimethyl-3-oxopropanoate (41b): 4.96 g (15.6 mmol, 52%); IR (thin film) 1740, 1698, 1387, 1369, 965 cm^{-1}; ^{1}H NMR δ 7.59 (d, 1 H, J = 7.8 Hz), 7.38 (m, 1 H), 7.25 (m, 2 H), 6.58 (d, 1 H, J = 15.8 Hz), 6.25 (dt, 1 H, J = 15.8, 7.1 Hz), 4.17 (q, 2 H, J = 7.1 Hz), 3.65 (s, 3 H), 3.24 (dd, 2 H, J = 7.1, 1.5 Hz), 1.49 (s, 6 H), 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 204.3, 174.2, 171.3, 137.1, 135.6, 130.9, 130.2, 127.0, 126.7,

125.4, 124.7, 60.8, 55.8, 52.4, 38.4, 23.5, 14.2; HRMS *m/e* for $C_{18}H_{22}O_5$: calcd 318.1467. Found: 318.1463.

Methyl (*E*)-3-(2-(3-Ethoxycarbonyl-2-propenyl) phenyl)-2,2-dimethyl-3-oxopropanoate (41a): 1.82 g (5.72 mmol, 19%); IR (thin film) 1740, 1721, 1695, 1655, 1385, 1368 cm^{-1}; ^1H NMR δ 7.37 (m, 2 H), 7.25 (m, 2 H), 7.07 (dt, 1 H, *J* = 15.7, 6.7 Hz), 5.75 (d, 1 H, *J* = 15.7 Hz), 4.16 (q, 2 H, *J* = 7.1 Hz), 3.63 (m, 2 H), 3.61 (s, 3 H), 1.50 (s, 6 H), 1.26 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 203.1, 174.6, 166.4, 147.0, 137.4, 137.2, 131.5, 130.9, 126.3, 126.2, 122.5, 60.2, 55.3, 52.4, 36.1, 24.0, 14.2; HRMS *m/e* for $C_{18}H_{22}O_5$: calcd 318.1467. Found: 318.1466.

Ethyl (*E*)-3-(2-(3-Methoxycarbonyl-3-methyl-2-oxobutyl) phenyl) propenoate (42): 6.11 g (19.2 mmol, 78%); IR (thin film) 1750, 1720, 1639, 1391, 1371, 767 cm^{-1}; ^1H NMR δ 7.73 (d, 1 H, *J* = 15.7 Hz), 7.61 (m, 1 H), 7.33-7.27 (complex, 2 H), 7.10 (m, 1 H), 6.36 (d, 1 H, *J* = 15.7 Hz), 4.24 (q, 2 H, *J* = 7.1 Hz), 3.97 (s, 2 H), 3.80 (s, 3 H), 1.49 (s, 6 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 204.5, 174.0, 166.7, 141.6, 134.2, 133.5, 131.2, 129.9, 127.7, 126.7, 120.2, 60.4, 55.6, 52.7, 42.2, 22.3, 14.3; HRMS *m/e* for $C_{18}H_{22}O_5$: calcd 318.1467. Found: 318.1461.

1-Ethyl Methyl (*E*)-7,7-Dimethyl-6-oxo-2-octenedioate (43): 4.82 g (18.8 mmol, 58%); IR (thin film) 1751, 1735, 1720, 1663, 1392, 1374 cm^{-1}; ^1H NMR δ 6.90 (dt, 1 H, *J* = 15.7, 6.8 Hz), 5.83 (d, 1 H, *J* = 15.7 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.73 (s, 3 H), 2.63 (t, 2 H, *J* = 6.8 Hz), 2.49 (m, 2 H), 1.38 (s, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 206.2, 173.8, 166.3, 146.8, 122.1, 60.1, 55.3, 52.4, 36.1, 26.1, 21.8, 14.3; HRMS *m/e* for $C_{13}H_{20}O_5$: calcd 256.1311. Found: 256.1309.

Representative Procedure for the Tandem Dealkoxycarbonylation-Michael Reaction: Ethyl (±)-2,2-Dimethyl-3-oxocyclohexaneacetate (44). The general procedure of Bunce and co-workers[60] was used. To a flame-dried three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser, and a

rubber septum was added 170 mg (4 mmol) of dry LiCl and 270 mg (1 mmol) of **38**. HMPA (10 mL) was added via syringe, and the reaction mixture was stirred at rt to dissolve the LiCl. Once homogeneous, the reaction was heated for 4 h in an oil bath which had been preheated to 120 °C (± 5 °C). The reaction was cooled, added to 1.0 *M* HCl, and extracted with ether (2x). The combined organic layers were washed with 1.0 *M* HCl, H_2O, and NaCl, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by PTLC, eluting with increasing concentrations of ether in hexanes, to afford 157 mg (0.74 mmol, 74%) of **23**. IR (thin film) 1745, 1720, 1390, 1375 cm^{-1}; ^1H NMR δ 4.14 (q, 2 H, *J* = 7.1 Hz), 2.47 (m, 2 H), 2.38 (m, 1 H), 2.16 (m, 2 H), 1.98 (m, 1 H), 1.84 (m, 1 H), 1.80-1.55 (complex, 2 H), 1.26 (t, 3 H, *J* = 7.1 Hz), 1.14 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR δ 215.0, 173.0, 60.5, 48.3, 44.1, 37.8, 35.7, 27.0, 22.9, 20.1, 15.3, 14.2; HRMS *m/e* for $C_{12}H_{20}O_3$ calcd 212.1412, found 212.1417.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 68.03; H, 9.40.

Other compounds prepared using this procedure, though on different scales, are given below. The compounds were purified by silica gel column chromatography or PTLC eluted with increasing concentrations of diethyl ether in hexanes.

Ethyl (±)-10-Oxospiro[4.5]decane-6-acetate (45): 150 mg (0.63 mmol, 63%); IR (thin film) 1738, 1705 cm^{-1}; ^1H NMR δ 4.13 (q, 2 H, *J* = 7.1 Hz), 2.51 (m, 1 H), 2.42-2.13 (complex, 5 H), 1.94 (m, 2 H), 1.80 (m, 1 H), 1.57 (m, 6 H), 1.37-1.23 (complex, 2 H), 1.25 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 213.8, 172.9, 60.6, 60.4, 44.1, 38.0, 35.3, 34.9, 31.8, 27.3, 25.5 (2), 23.3, 14.2; HRMS *m/e* for $C_{14}H_{22}O_3$: calcd 238.1569. Found: 238.1564.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.58; H, 9.24. Found: C, 70.55; H, 9.22.

Ethyl (±)-5-Oxospiro[5.5]undecane-1-acetate (46): 151 mg (0.58 mmol, 60%); IR (thin film) 1740, 1710, 1380 cm^{-1}; ^1H NMR δ 4.12 (q, 2 H, *J* = 7.1 Hz), 2.48 (m, 2 H), 2.35 (m, 2 H), 2.06 (m, 4 H), 1.92 (m, 1 H), 1.84 (m, 1 H), 1.65-1.12 (complex, 9 H), 1.25 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 216.1, 173.2, 60.5, 52.6, 44.0,

38.0, 34.2, 33.6, 29.7, 26.0, 25.0, 24.4, 22.6, 22.3, 14.2; HRMS *m/e* for $C_{15}H_{24}O_3$: calcd 252.1725. Found: 252.1728.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52. Found: C, 71.37; H, 9.55.

Ethyl (±)-1,2,3,4-Tetrahydro-3,3-dimethyl-4-oxo-2-naphthaleneacetate (47): 120 mg (0.46 mmol, 46%); IR (thin film) 1735, 1680, 1600, 1382, 740 cm^{-1}; ^1H NMR δ 8.02 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.45 (t, 1 H, *J* = 7.5 Hz), 7.31 (t, 1 H, *J* = 7.1 Hz), 7.21 (d, 1 H, *J* = 7.2 Hz), 4.16 (q, 2 H, *J* = 7.1 Hz), 3.12 (dd, 1 H, *J* = 17.1, 4.3 Hz), 2.84 (dd, 1 H, *J* = 17.1, 8.7 Hz), 2.57 (m, 2 H), 2.23 (m, 1 H), 1.29 (s, 3 H), 1.27 (t, 3 H, *J* = 7.1 Hz), 1.10 (s, 3 H); ^{13}C NMR δ 201.9, 172.7, 141.2, 133.3, 130.8, 128.8, 127.9, 126.8, 60.6, 45.0, 40.5, 35.4, 31.3, 23.1, 19.4, 14.2; HRMS *m/e* for $C_{16}H_{20}O_3$: calcd 260.1412. Found: 260.1412

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.78; H, 7.66.

Ethyl (±)-1,2,3,4-Tetrahydro-2,2-dimethyl-3-oxo-1-naphthalene-acetate (48): 163 mg (0.63 mmol, 63%); IR (thin film) 1740, 1718, 1390, 1375, 760 cm^{-1}; ^1H NMR δ 7.23-7.10 (complex, 4 H), 4.04 (m, 2 H), 3.68 (A of ABq, 1 H, *J* = 21.0 Hz), 3.61 (B of ABq, 1 H, *J* = 21.0 Hz), 3.33 (m, 1 H), 2.68 (dd, 1 H, *J* = 15.1, 4.8 Hz), 2.26 (dd, 1 H, *J* = 15.1, 9.9 Hz), 1.16 (s, 3 H), 1.15 (t, 3 H, *J* = 7.1 Hz), 1.06 (s, 3 H); ^{13}C NMR δ 213.1, 172.1, 138.0, 132.4, 128.4, 128.1, 127.1, 126.8, 60.6, 48.1, 46.9, 42.2, 37.1, 25.5, 20.8, 14.1; HRMS *m/e* for $C_{16}H_{20}O_3$: calcd 260.1412. Found: 260.1406.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.69; H, 7.71.

Ethyl (±)-2,2-Dimethyl-3-oxocyclopentaneacetate (49): 48 mg (0.24 mmol, 24%); IR (thin film) 1740, 1390, 1372 cm^{-1}; ^1H NMR δ 4.17 (q, 2 H, *J* = 7.1 Hz), 2.49-2.36 (complex, 2 H), 2.30-2.14 (complex, 4 H), 1.55 (m, 1 H), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.05 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 222.4, 172.6, 60.6, 47.5, 43.7, 36.1, 35.1, 25.1, 22.5, 18.1, 14.2; HRMS *m/e* for $C_{11}H_{18}O_3$: calcd 198.1256. Found: 198.1255.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.41; H, 9.21.

Ethyl (*E*)-7-Methyl-6-oxo-2-octenoate (50): 103 mg (0.52 mmol, 52%); IR (thin film) 1730, 1710, 1660, 1390, 1372, 975 cm^{-1}; ^1H NMR δ 6.94 (dt, 1 H, *J* = 15.6, 6.8 Hz), 5.83 (d, 1 H, *J* = 15.6 Hz), 4.18 (q, 1 H, *J* = 7.1 Hz), 2.61 (m, 3 H), 2.47 (q, 2 H, *J* = 6.8 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.11 (d, 3 H, *J* = 6.9 Hz), ^{13}C NMR δ 212.7, 166.4, 147.4, 121.9, 60.2, 40.8, 38.1, 26.0, 18.1, 14.2; HRMS *m/e* for $C_{11}H_{18}O_3$: calcd 198.1256. Found: 198.1251.

Chapter 5

A Tandem Dealkoxycarbonylation-Michael Addition Route to Five- and Six-membered Lactams and Lactones.

Results

The starting materials for the heterocyclic cyclization substrates required two specific functional groups to make them suitable for the tandem dealkoxycarbonylation-heterocyclization developed in our lab. The starting compounds **1** needed a heteroatom that could participate in an acylation reaction. This reaction allowed the attachment of the dimethyl methyl ester chain as illustrated in Figure 1.

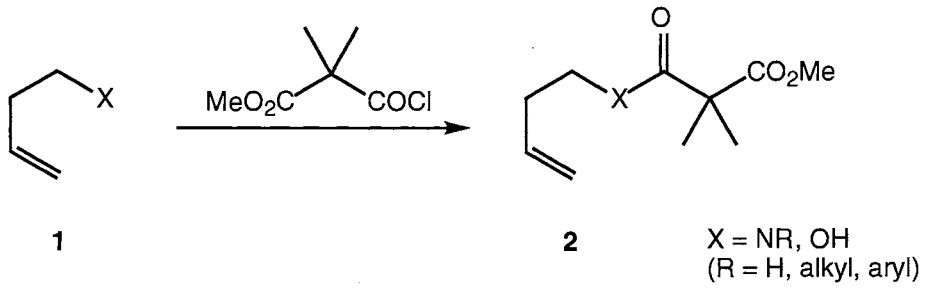


Figure 1. Acylation Reaction of Heteroatom Starting Compounds.

Secondly, the starting materials required a suitably positioned double bond that could be transformed, via an ozonolysis-Wittig[60] sequence (Figure 2), to an ethyl acrylate moiety as in compound **3**.

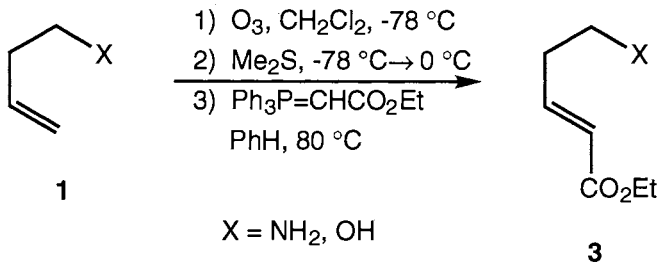


Figure 2. Ozonolysis/Wittig Reaction to Add Ethyl Acrylate Functionality.

To this end, a variety of starting materials were converted by this strategy, using variations where necessary, to afford a series of heterocyclic cyclization substrates.

Synthesis of Lactone Precursors

Commercially available 3-butenol (**4**) was acylated, using the acid chloride derived from the monomethyl ester of dimethylmalonic acid,[98] under standard acylation conditions (Figure 3) to afford the dimethyl propanedioate **5**. The unsaturated ester was then subjected to ozonolysis followed by reductive workup to give the crude aldehyde which was used without further purification. Wittig olefination of the aldehyde afforded the lactone cyclization precursor **7** to the six-membered lactone.

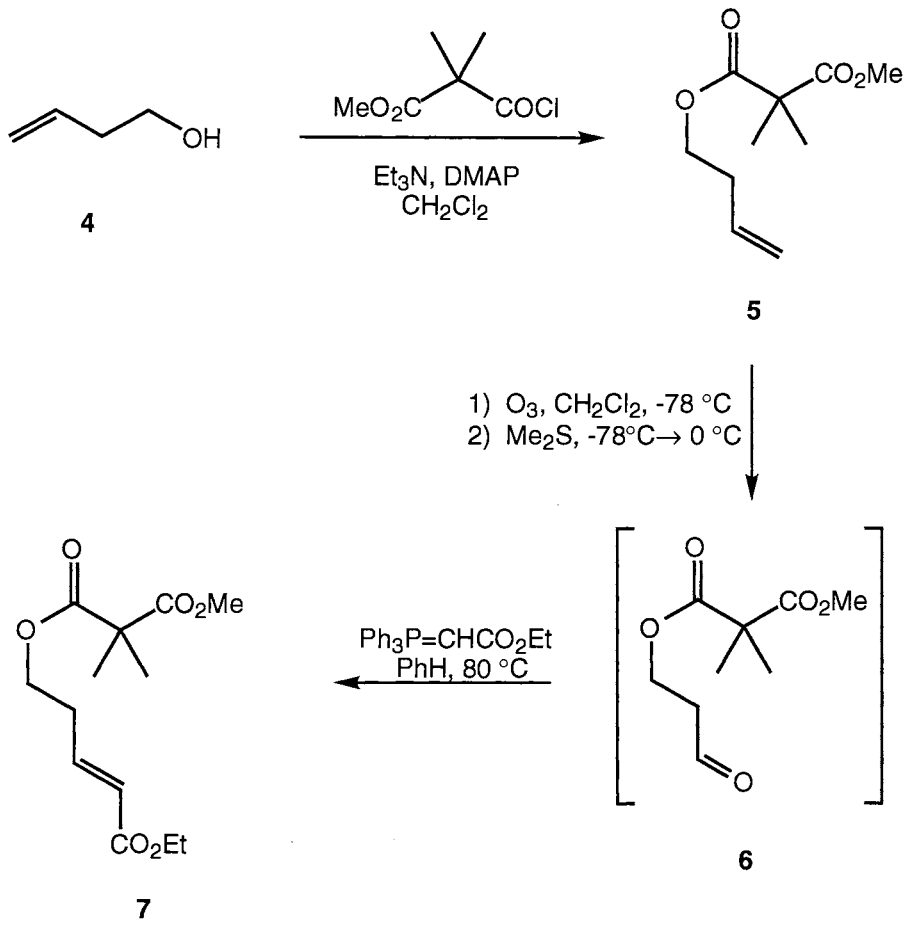


Figure 3. Synthesis of Precursor to Six-Membered Lactone.

The desire to generate fused aromatic heterocycles initiated a search for aromatic starting materials containing the requisite functionality. A hydroxy benzaldehyde would have shortened the synthetic pathway to the cyclization substrate by one step because it already possessed the aldehyde functionality. Figure 4 illustrates the conversion of an ideal candidate, 2-hydroxybenzaldehyde. Starting with commercially available 2-hydroxy-benzaldehyde **8**, Wittig olefination introduced the ethyl acrylate moiety generating the propenoate derivative **9**. Subsequent acylation using previously established conditions afforded the precursor **10** to the fused aromatic lactone product.

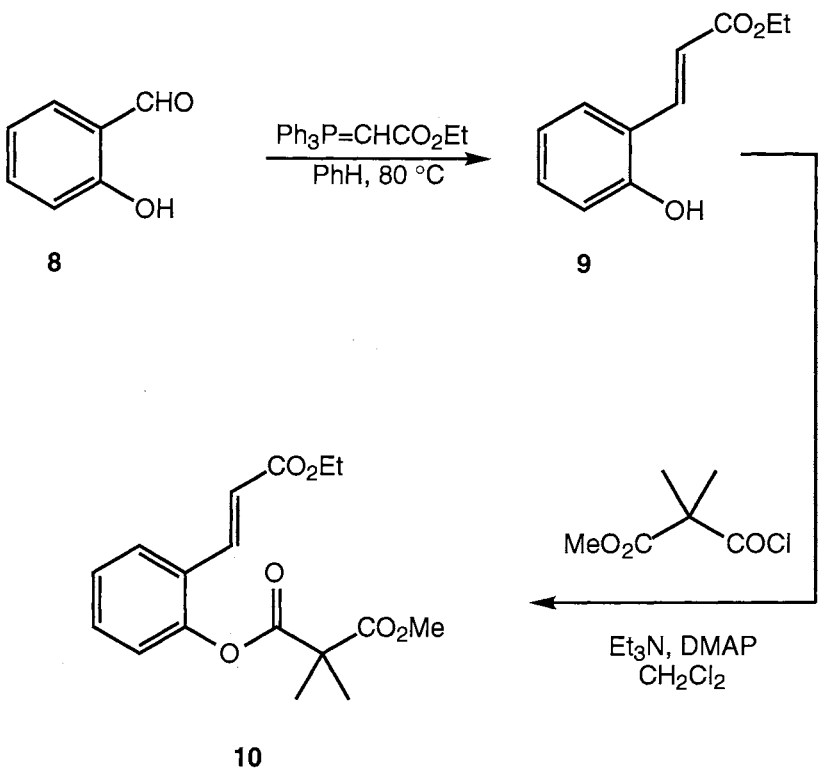


Figure 4. Synthesis of Precursor to Fused Aromatic Lactone.

Additional compounds were sought that had other functionality in addition to the hydroxyl and aldehyde groups. A quick search of standard commercial sources indicated two compounds meeting these requirements. Starting with commercial 2-hydroxy-1-naphthaldehyde (Figure 5), Wittig olefination yielded the propenoate derivative **6**. Using the developed acylation conditions added the dimethyl methyl ester side chain giving the dimethylpropanedioate diester derivative **7**.

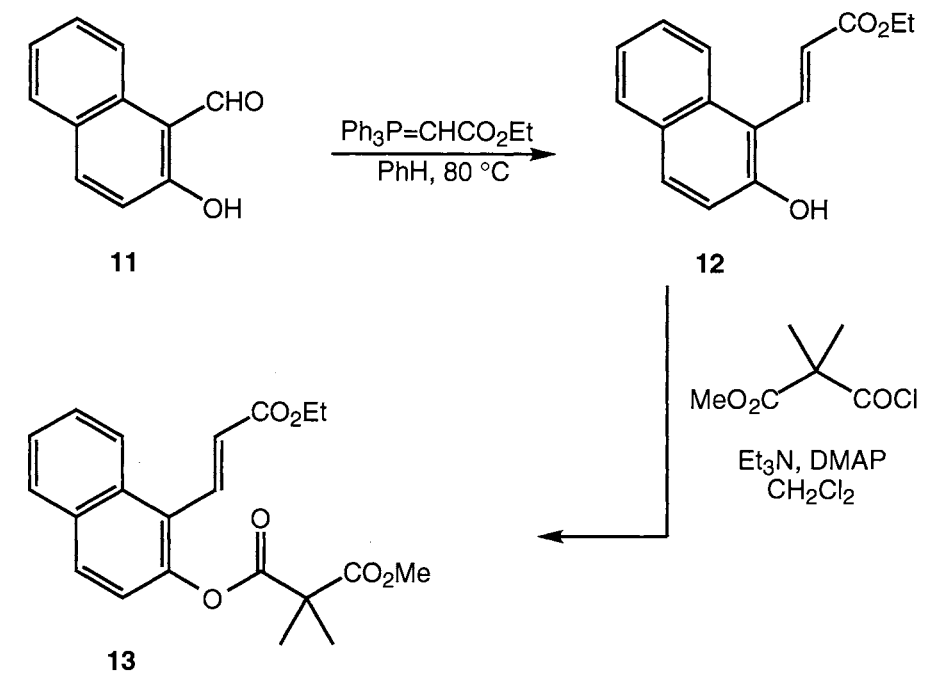


Figure 5. Synthesis of Precursor to 5,6-Benzo-Fused Lactone.

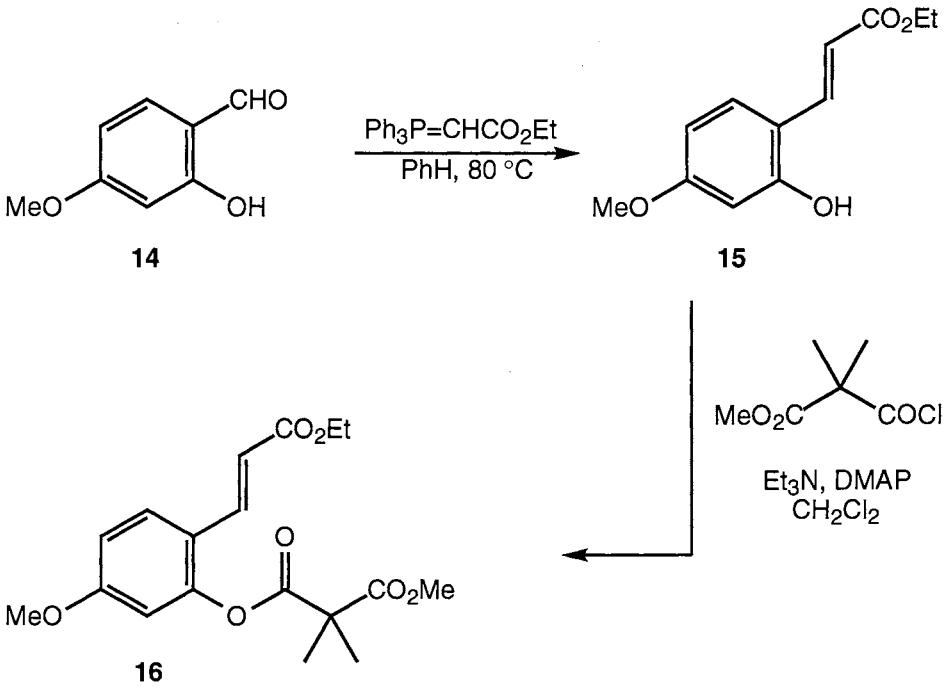


Figure 6. Synthesis of Precursor to Methoxy-Substituted Lactone.

Similarly, Figure 6 illustrates the conversion of commercially available 4-methoxy-2-hydroxybenzaldehyde **14** to the propenoate derivative **15** and subsequently to the cyclization substrate **16**.

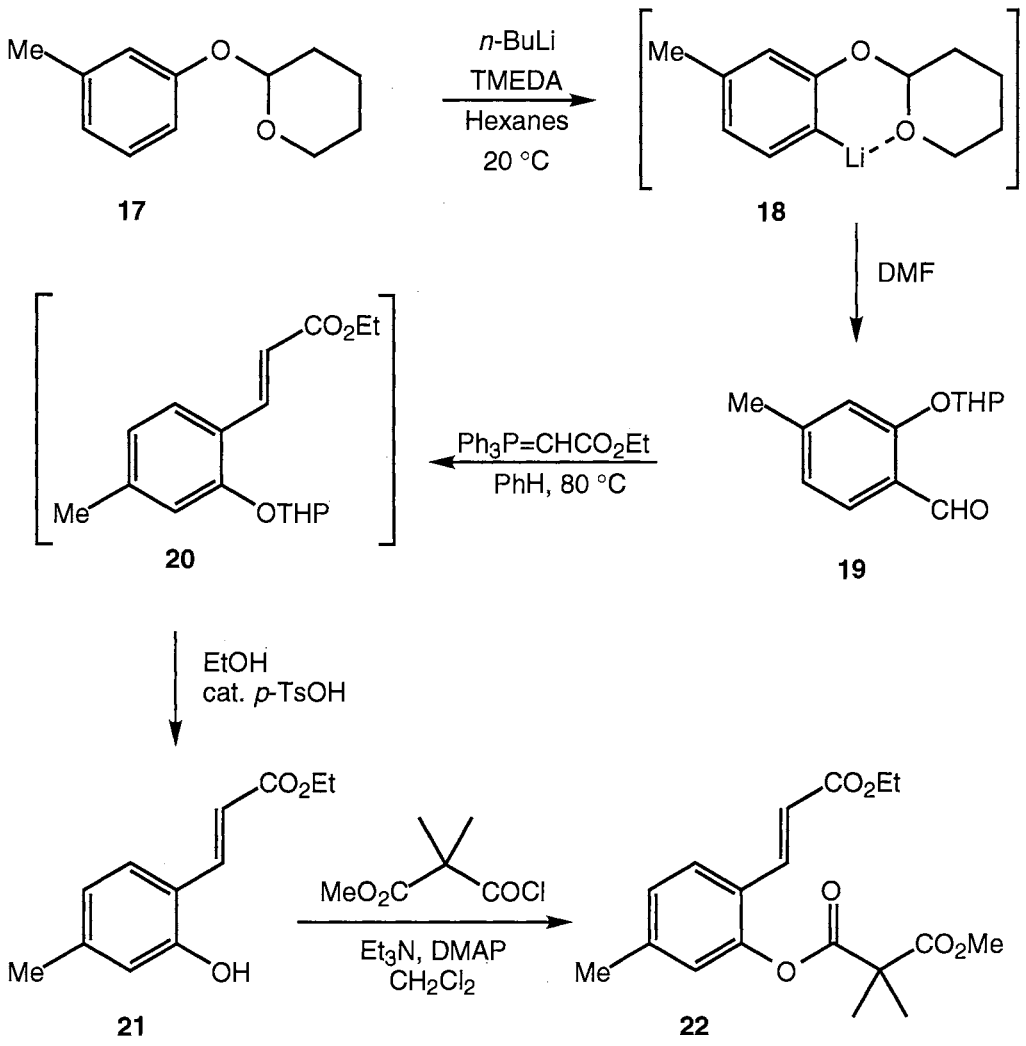


Figure 7. Synthesis of Precursor to Methyl-Substituted Lactone.

The search for a commercially available 2-hydroxybenzaldehyde that was substituted with an alkyl group proved fruitless. Concurrent research[99] in our laboratory, however, was concerned with the synthesis of *o*-hydroxycinnamate esters as starting

compounds for another project. This research provided a source of alkyl-substituted *o*-hydroxycinnamate esters which could then be converted to cyclization substrates. Figure 7 outlines the procedure for the synthesis of **17**. Starting with commercially available 3-methylphenol the THP ether **17** was obtained by reaction with 2 equivalents of dihydropyran and catalytic *p*-TsOH in $CHCl_3$. Lithiation of **17** using 1.1 equivalents of *n*-BuLi-TMEDA in hexanes at 0 °C afforded the *o*-lithiated intermediate **18** in a 12.5 : 1 excess over the other possible *ortho* isomer. Quenching of the lithiated species with DMF gave the aldehyde derivative **19** as the major product. Wittig olefination converted the aldehyde to the protected *o*-hydroxycinnamate **20** which was not isolated but rather deprotected using catalytic *p*-TsOH in EtOH to give the hydroxy compound **21**. Subsequent acylation of **21** afforded the methyl-substituted cyclization substrate **22**.

Tandem Dealkoxycarbonylation-Michael Addition Reaction of Lactone Precursors.

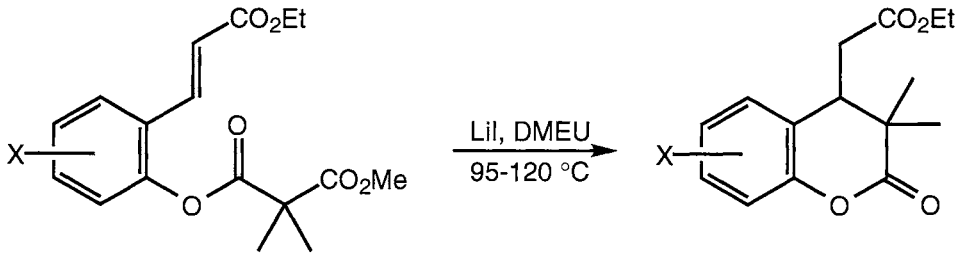
Cyclization Substrate	Yield, (%) [a]
7	43
10	62
13	59
16	61
22	35

[a] Yields refer to isolated purified products

Table 1. Yields of Lactone Precursors.

The strategy for adding the requisite functionality to the cyclization substrates was applied to a series of starting materials. The overall yields of the cyclization substrates are compiled in Table 1.

Results of Lactone Cyclization Reactions



10 (X = H)
13 (X = 4,5-benzo)
16 (X = 3-OMe)
22 (X =3-Me)

23 (X = H)
24 (X = 4,5-benzo)
25 (X = 3-OMe)
26 (X = 3-Me)

Figure 8. General Tandem Dealkoxycarbonylation-Michael Addition Reaction of Lactone Precursors.

With the cyclization substrates in hand, a number of cyclizations were undertaken. The reaction conditions developed previously for the carbocyclic project[75] were tried first. Given the hazardous nature of HMPA, alternate solvents were tried. The best results were achieved using DMEU with LiI as the nucleophile. The original nucleophile used in the carbocycle project, LiCl, did not perform well with DMEU and was subsequently replaced by LiI for all of the heterocyclizations. This solvent/nucleophile combination provided an additional benefit in that it allowed the use of lower reaction temperatures to effect the tandem reaction. Using HMPA and LiCl, the reactions were run at 120 °C. With DMEU and LiI, reaction temperatures were between 95-120 °C. Figure 8 illustrates the general tandem dealkoxycarbonylation-Michael addition sequence that affords the heterocyclic

products. The straight chain cyclization substrates where the oxygen is not attached to an aromatic ring failed to cyclize. Analysis of the reaction mixtures indicated that the cyclization substrate decomposed into several unidentifiable components and did not produce any ring-closed product. In the aromatic cases, all of the cyclization products were accompanied by a fairly constant quantity of an identifiable byproduct **16a**. The byproduct was one where the diester side chain had been cleaved and replaced with a methyl group. A possible mechanism for the reaction is illustrated in Figure 9. Further experiments using aniline to trap the dimethyl ketene **31** (Figure 10) *in situ* have indicated the presence of the trapped product **32**. The cyclized products, along with their respective yields are summarized in Table 2.

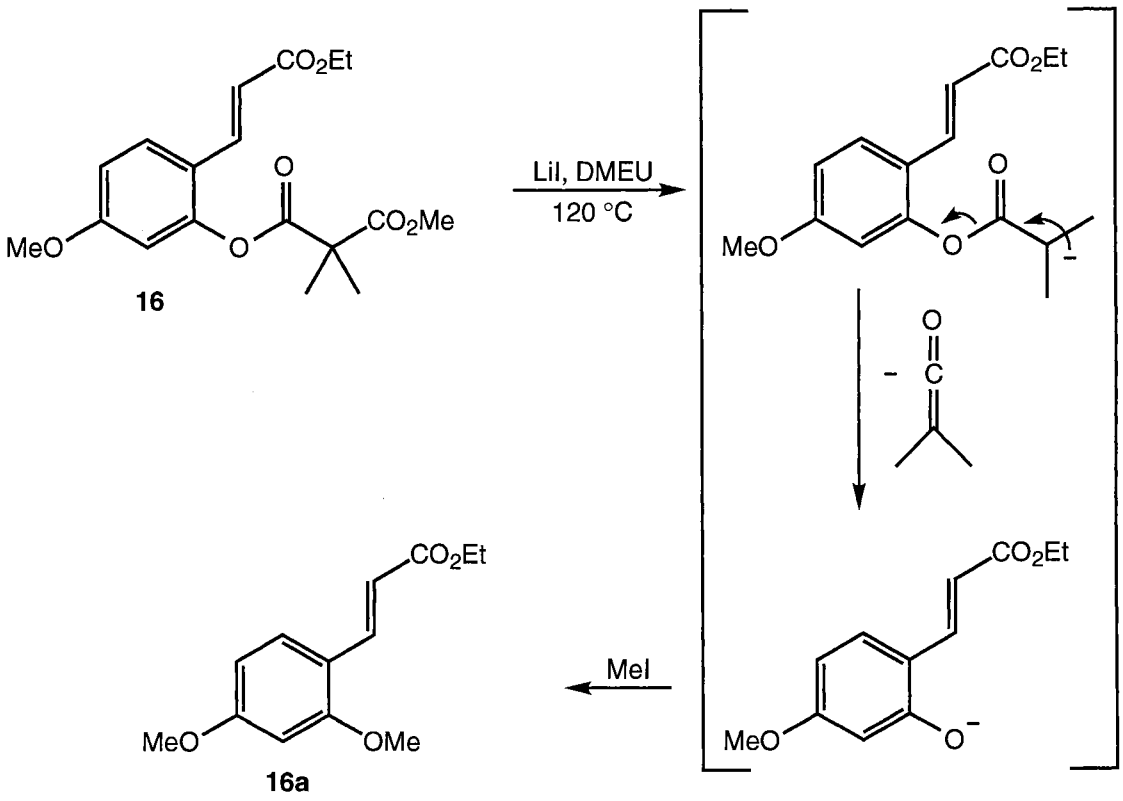
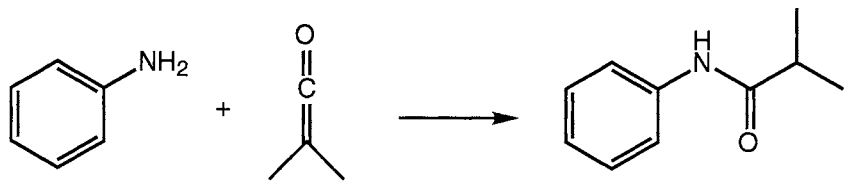


Figure 9. Possible Mechanism for Cyclization Byproduct Formation.



30 31 32

Figure 10. Trapping of Dimethyl Ketene *in situ* by Aniline.

Cyclization Substrate	Cyclization Product	Yield, (%) [a]
7	--	0
10	**23**	62
13	**24**	40
16	**25**	46
22	**26**	37

[a] Yields refer to isolated purified products.

Table 2. Cyclization Yields of Lactone Precursors.

Synthesis of Lactam Precursors

Using the methodology developed for the closure of oxygen heterocycles, the lactam cyclization substrates would be accessible provided the appropriate starting materials could be obtained. Alkenylamines are common and synthetically available via the Gabriel synthesis.[100] Figure 11 illustrates the conversion of the 3-butenylamine **33**, via acylation, to the amide derivative **34**. Subsequent ozonolysis followed by Wittig olefination afforded the lactam precursor **36**.

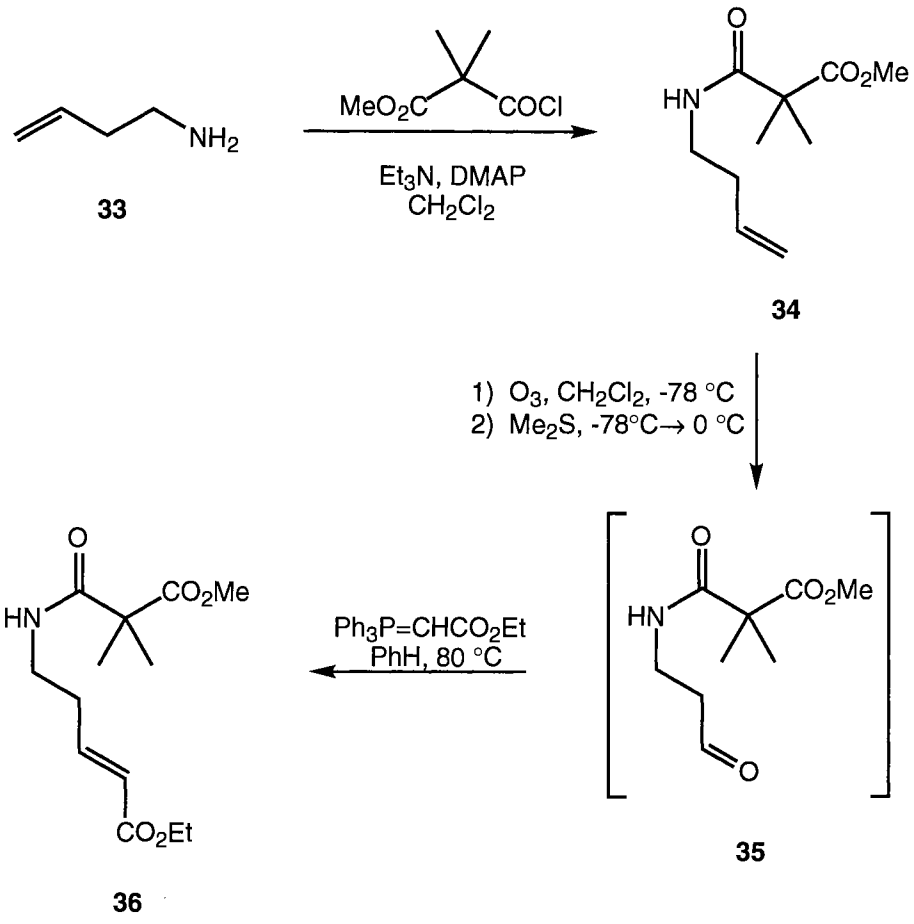


Figure 11. Synthesis of Precursor to Six-Membered Lactam.

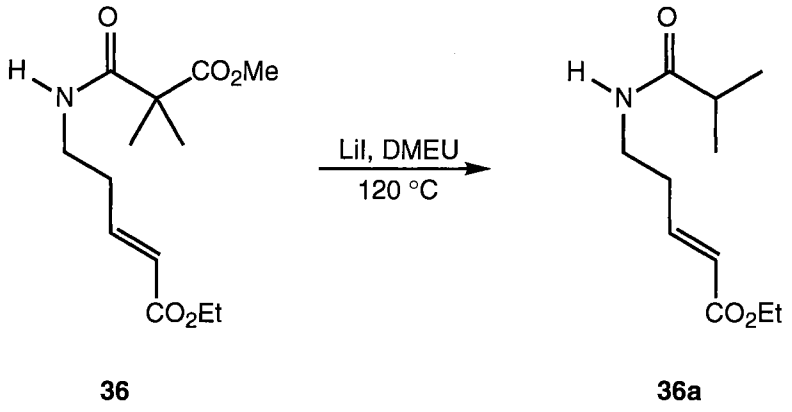


Figure 12. Uncyclized Major Product from Lactam Cyclization.

Knowing that the tandem dealkoxycarbonylation-Michael addition reaction proceeds through a stabilized carbanion there was some concern about the presence of a moderately acidic proton in the lactam cyclization substrate. Initial attempts at cyclizing the unprotected nitrogen substrate yielded one major product that was uncyclized. The structure of the product was elucidated by ^{1}H NMR to be **36a** (Figure 12) and Figure 13 illustrates a possible mechanism for it's formation.

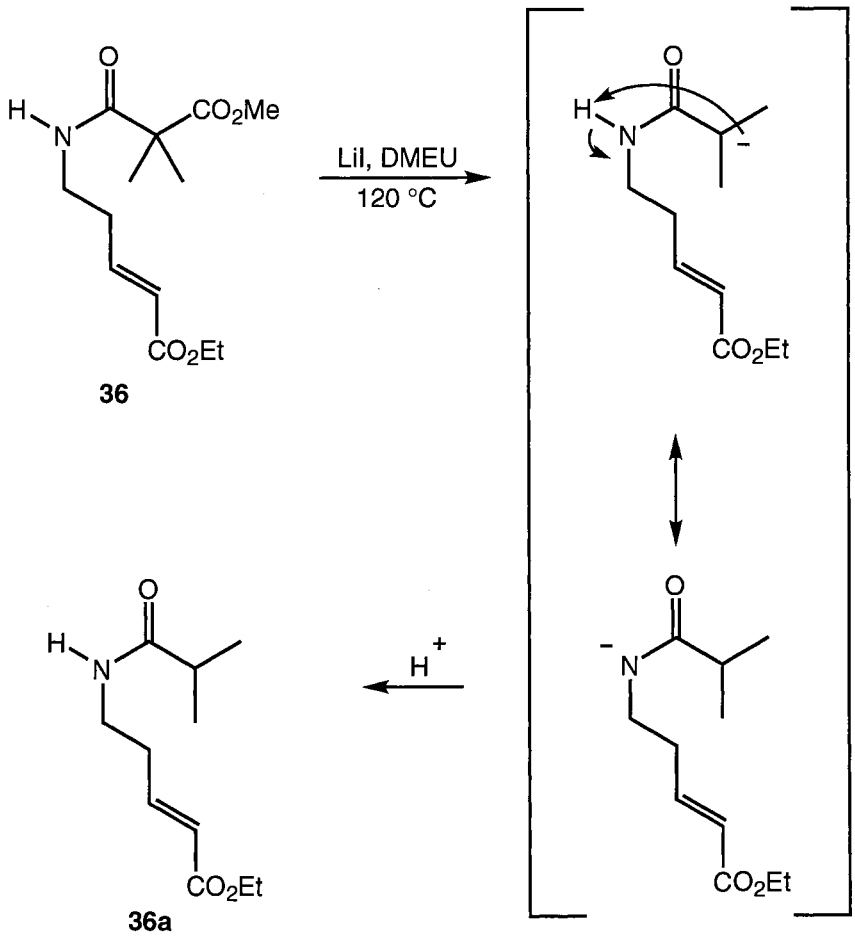


Figure 13. Possible Mechanism for Cyclization Byproduct Formation.

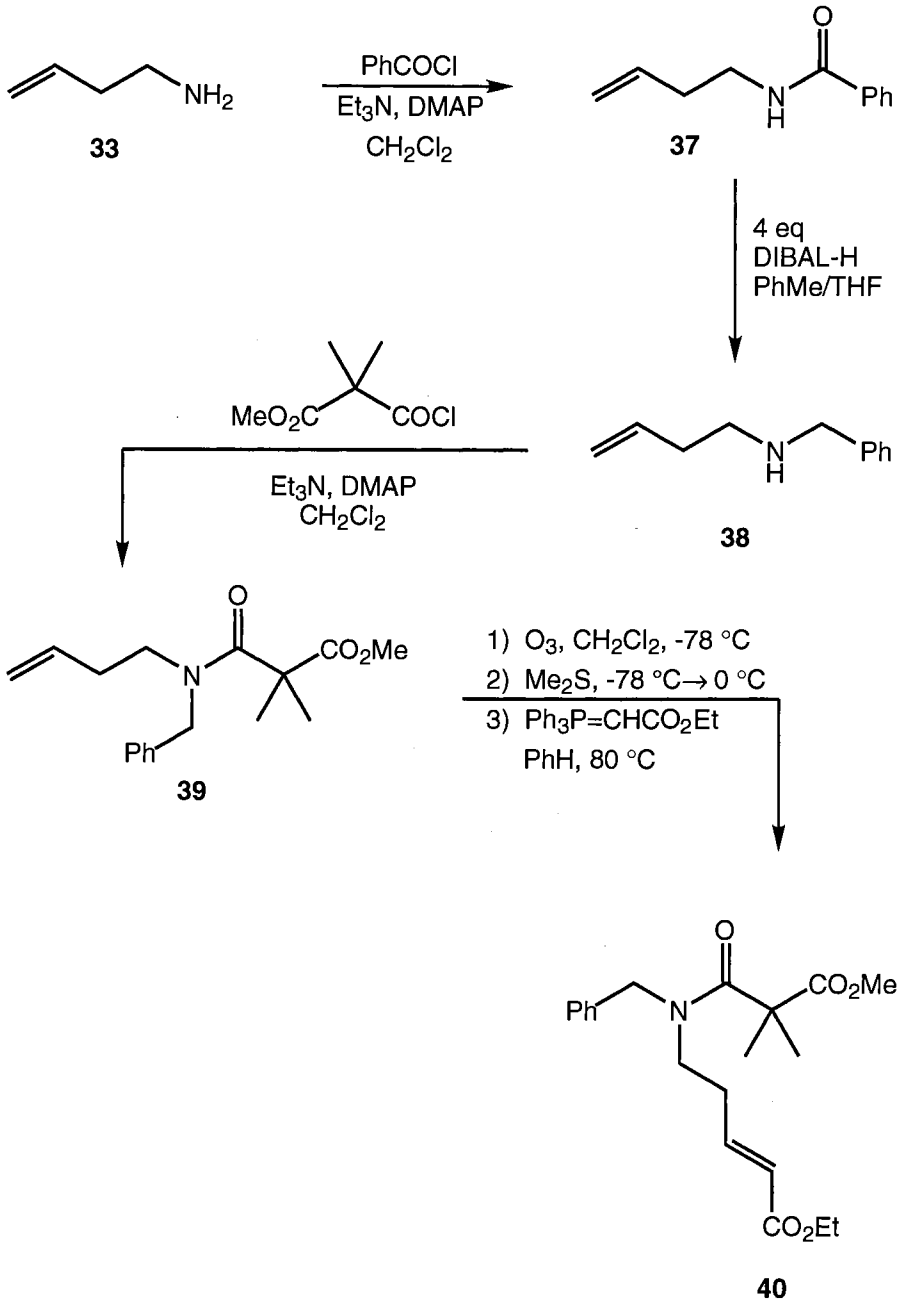


Figure 14. Synthesis of Precursor to Benzyl-Protected Lactam.

The problem with the moderately acidic proton was addressed by synthesizing two precursors where the acidic proton was replaced by protecting groups. Synthesis of a benzyl-protected substrate is outlined in Figure 14. Again, starting from the 3-

butenylamine **33**, acylation with benzoyl chloride under standard conditions gave the alkenyl benzamide **37**. Reduction[101] using four equivalents of DIBAL-H afforded the benzyl butenyl amine **38**. Acylation with methyl dimethylmalonyl chloride yielded the propanoate **39** which was then subjected to Wittig olefination to afford the benzyl protected lactam cyclization substrate **40**. Initial attempts at cyclizing the benzyl-protected lactam precursor were not successful, possibly owing to iodide-promoted nucleophilic dealkylation of the amide.

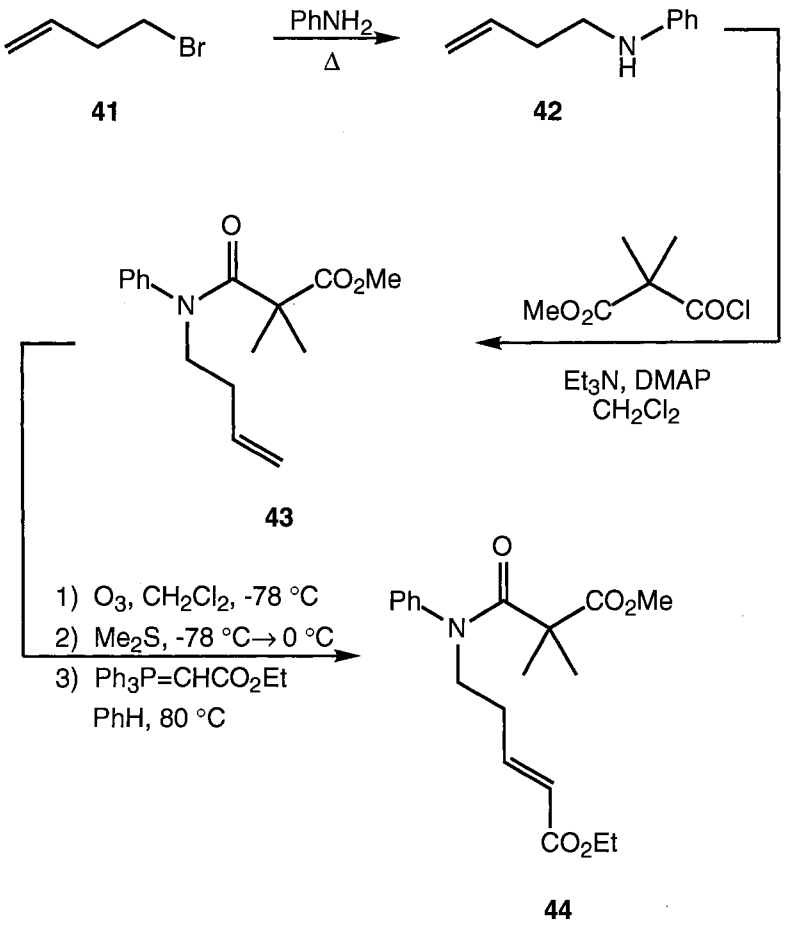


Figure 15. Synthesis of Precursor to Phenyl-Protected Lactam.

The third protected lactam precursor utilized a phenyl group on the nitrogen. In Figure 15 the known 4-bromobutene (**41**) was alkylated by refluxing in excess aniline. The resulting butenyl aniline **42** was then acylated with methyl dimethylmalonyl chloride to obtain the propanedioate derivative **43**. Subsequent Wittig olefination afforded the phenyl-protected lactam precursor **44**. Cyclizations using this compound were successful (*vide infra*) establishing the *N*-phenyl amides as substrates worthy of further investigation.

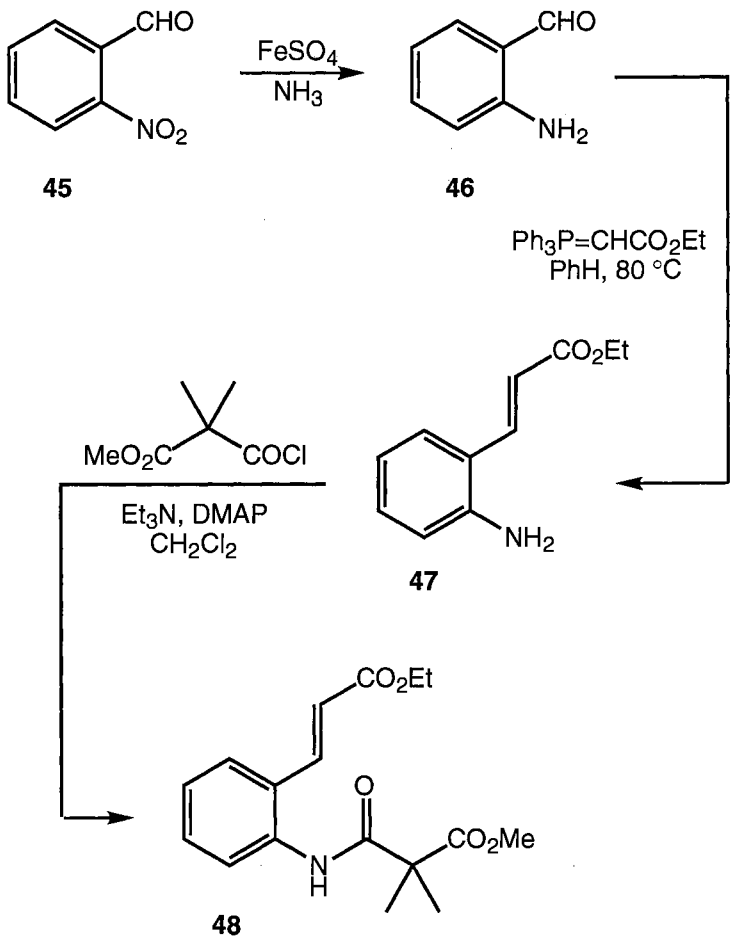


Figure 16. Synthesis of Precursor to Fused Aromatic Lactam.

Drawing on the success of the fused aromatic lactone cyclizations a search was conducted for a suitable starting material to synthesize fused aromatic lactam cyclization

substrates. Unfortunately, 2-aminobenzaldehyde was not commercially available due to it's instability. Synthetically, 2-aminobenzaldehyde (**46**) was easily accessible from 2-nitrobenzaldehyde (**45**).[102] Figure 16 outlines the conversion of 2-nitrobenzaldehyde (**45**) to the desired fused aromatic lactam precursor. The commercially available 2-nitrobenzaldehyde was reduced using $FeSO_4$ in ammonia to give 2-aminobenzaldehyde (**46**). The aminobenzaldehyde was subjected to Wittig olefination to give the 2-aminophenyl propenoate derivative **47**. Subsequent acylation with methyl dimethylmalonyl chloride afforded the lactam precursor **48**.

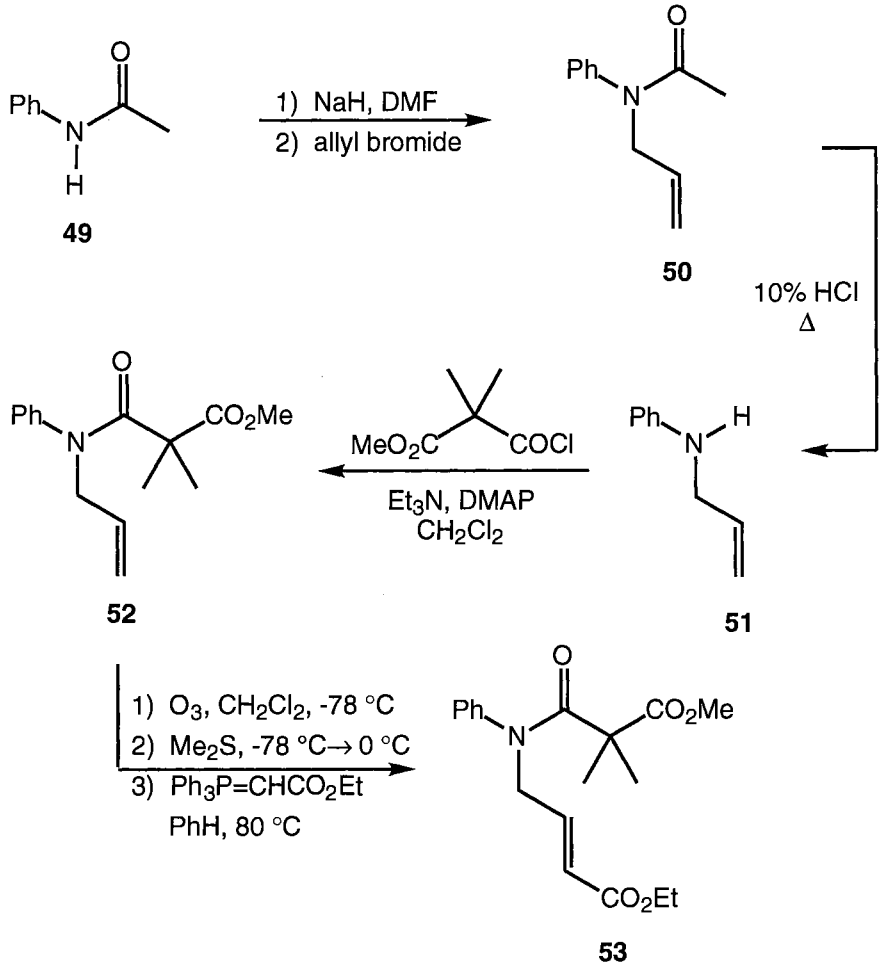


Figure 17. Synthesis of Precursor to Five-Membered Lactam.

Remembering the success of the five-membered ring closure in the carbocycle project,[74] a phenyl-protected five-membered lactam precursor was synthesized (see Figure 17). Acetanilide (**49**) was alkylated with allyl bromide using standard conditions to give the amide derivative **50**. Hydrolysis in aqueous HCl removed the acyl group yielding the allylphenylamine (**51**). Acylation with dimethyl methylmalonyl chloride generated the propenoate derivative **52** and subsequent Wittig olefination afforded the five-membered lactam cyclization substrate **53**.

The same general methodology was applied to a series of starting materials. The overall yields of the lactam precursors are summarized in Table 3.

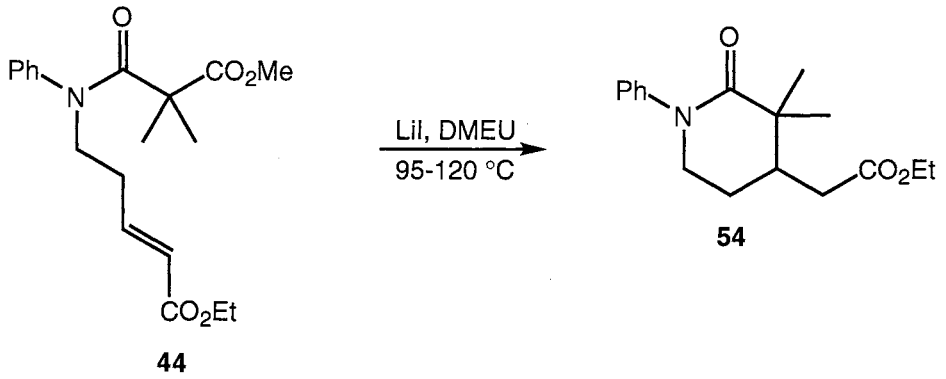
Cyclization Substrate	Yield, (%) [a]
36	41
40	35
44	43
48	53
53	37

[a] Yields refer to isolated purified products.

Table 3. Yields of Lactam Precursors.

The phenyl-substituted lactam precursors were cyclized using the same general conditions applied to the lactone cyclizations. LiI was used with DMEU as the solvent. Again, certain cyclizations could be effected with lower temperatures than those used in the carbocycle project. Figure 18 illustrates the general tandem dealkoxycarbonylation-Michael addition reaction of lactam cyclization substrate **44** to piperidinone product **54**. The general cyclization protocol was applied to all of the cyclization substrates. The

unprotected and benzyl-protected precursors yielded only uncyclized material. The overall yields of the lactam cyclizations are listed in Table 4.



44 **54**

Figure 18. General Tandem Dealkoxycarbonylation-Michael Addition Reaction of Lactam Precursors.

Cyclization Substrate	Cyclized Product	Yield, (%) [a]
36	--	0
40	--	0
44	**54**	82
48	**55**	76
53	**56**	30

[a] Yields refer to isolated purified products.

Table 4. Yields of Lactam Cyclizations.

Conclusion

From the results presented, it is obvious that the synthetic methodology has broad potential for accessing heterocyclic systems. The pool of possible starting materials is sizeable and the final products need not be restricted to simple or fused aromatic heterocycles. Heterocyclic compounds are a common theme in the realm of natural products chemistry. The increased ability to access these systems is a benefit to both the synthetic chemist and the medical establishment as many heterocyclic compounds possess biological activity. This research shows current and future potential for expanding the knowledge of tandem reactions and their applicability to a variety of systems.

Experimental

Solvents were purified in the following manner: DMF and HMPA were stored under nitrogen over 4-Å molecular sieves, THF was distilled from $LiAlH_4$, and diisopropylamine was distilled from CaH_2. Other reagents were used as received. All reactions were run under dry N_2. Unless otherwise indicated, the saturated NH_4Cl, saturated $NaHCO_3$, 5% $Na_2S_2O_3$, saturated NaCl, and 0.5-1.0 *M* HCl used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) visualized using UV light, phosphomolybdic acid, or I_2 vapor or (2) capillary GC with FI detection (SE-30 column, 6-m x 0.25-mm i.d., 0.25-μm film thickness) programmed between 50-300°C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates[95] (Analtech), (2) flash chromatography[96] on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sylvania no. 2282), (3) flash vacuum chromatography[97] on silica gel (60-200 mesh). Band elution, where appropriate, was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra are referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured

in $CDCl_3$ at 400 and 100 MHz, respectively, and are referenced to internal $(CH_3)_4Si$. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV. Elemental analyses are ± 0.3%.

Methyl Dimethylmalonyl Chloride. This compound was prepared as needed by reacting the monomethyl ester of dimethylmalonic acid[98] with a 20% excess of thionyl chloride in refluxing benzene for 6 h. Removal of the solvent under vacuum gave a yellow oil which was used directly for the synthesis of esters and amides. IR (thin film) 1810, 1751, 1391, 1377, 755 cm^{-1}; ^1H NMR δ 3.80 (s, 3 H), 1.56 (s, 6 H); ^{13}C NMR δ 174.0, 170.7, 59.7, 53.0, 22.8.

3-Butenyl Methyl Dimethylpropanedioate (5). To a stirred 0 °C solution of 5.00 g (69.4 mmol) of 3-buten-1-ol, 10.6 g (14.6 mL, 105 mmol) of Et_3N, and 0.20 g of DMAP in 100 mL of CH_2Cl_2 was added a solution of 12.3 g (75.0 mmol) of methyl dimethylmalonyl chloride in 50 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by vacuum distillation through a 15-cm Vigreux column to afford 11.36 g (56.8 mmol, 82%) of the diester as a colorless oil, bp 78-80 °C (10 mm Hg). IR (thin film) 3076, 1640, 1642, 1390, 1369, 991, 918 cm^{-1}; ^1H NMR δ 5.75 (ddt, 1 H, J = 17.0, 10.1, 6.6 Hz), 5.10 (d, 1 H, J = 17.0 Hz), 5.07 (d, 1 H, J = 10.1 Hz), 4.18 (t, 2 H, J = 6.6 Hz), 3.71 (s, 3 H), 2.38 (q, 2 H, J = 6.6 Hz), 1.43 (s, 6 H); ^{13}C NMR δ 173.2, 172.7, 133.7, 117.3, 64.2, 52.4, 49.8, 32.9, 22.8; HRMS *m/e* for $C_{10}H_{16}O_4$: calcd 200.1049. Found: 200.1046.

Representative Ozonolysis/Wittig Procedure: (*E*)-4-Ethoxycarbonyl-3-butenyl Methyl Dimethylpropanedioate (7). A solution of 4.00 g (20.0 mmol) of 3-butenyl methyl dimethylpropanedioate in 150 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C

with 4.23 g (5.00 mL, 68.2 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 11.1 g (32.0 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 12 h, then cooled to rt and concentrated under vacuum to give a tan semisolid mass. The residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 15-20% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatography on a 40-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.37 g (12.4 mmol, 62%) of the triester as a light yellow oil. IR (thin film) 1738, 1721, 1660, 1390, 1369, 978 cm^{-1}; ^1H NMR δ 6.88 (dt, 1 H, J = 15.8, 6.9 Hz), 5.88 (d, 1 H, J = 15.8 Hz), 4.24 (t, 2 H, J = 6.3 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 3.72 (s, 3 H), 2.55 (dt, 2 H, J = 6.8, 6.3 Hz), 1.44 (s, 6 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 173.1, 172.6, 166.0, 143.6, 123.6, 63.0, 60.3, 52.4, 49.7, 31.1, 22.7, 14.2; HRMS *m/e* for $C_{13}H_{20}O_6$: calcd 272.1260. Found: 272.1262.

Ethyl (*E*)-3-(2-Hydroxyphenyl)propenoate (9). A mixture of 5.25 g (43.0 mmol) of salicylaldehyde and 31.3 g (90.0 mmol) of ethyl (triphenylphosphoranylidene)acetate in 300 mL of benzene was heated under reflux for 12 h. The reaction was cooled and concentrated to afford a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude hydroxy ester as a yellow oil which crystallized on standing. Final purification by flash chromatography on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 6.27 g (32.7 mmol, 76%) of the hydroxy ester as a white solid, mp 81-82 °C. IR (thin film) 3440, 1685, 1630, 1608, 1510, 1375, 758 cm^{-1}; ^1H NMR δ 8.06 (d, 1 H, J = 16.2 Hz), 7.46 (d, 1 H, J = 7.8 Hz), 7.24 (m, 1 H), 7.13 (br s, 1 H), 6.89 (m, 2 H), 6.66 (d, 1 H, J = 16.2 Hz), 4.29

(q, 2 H, J = 7.1 Hz), 1.35 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 168.7, 155.6, 140.9, 131.4, 129.2, 121.7, 120.6, 118.2, 116.4, 60.7, 14.3; HRMS *m/e* for $C_{11}H_{12}O_3$: calcd 192.0787. Found: 192.0788.

(*E*)-2-(2-Ethoxycarbonylethenyl)phenyl Methyl Dimethylpropanedioate (10). To a stirred 0 °C solution of 4.00 g (20.8 mmol) of ethyl (*E*)-3-(hydroxy phenyl)propenoate, 3.16 g (4.35 mL, 31.3 mmol) of Et_3N and 0.15 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 3.95 g (24.0 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the ma*J*or band gave 4.79 g (15.0 mmol, 72%) of the triester as a light yellow solid, mp 39-41 °C. IR (thin film) 1770, 1745, 1715, 1640, 1603, 1488, 1390, 1369, 759 cm^{-1}; ^{1}H NMR δ 7.75 (d, 1 H, J = 16.1 Hz), 7.66 (d, 1 H, J = 8.0 Hz), 7.40 (t, 1 H, J = 7.4 Hz), 7.27 (t, 1 H, J = 7.5 Hz), 7.07 (d, 1 H, J = 8.1 Hz), 6.44 (d, 1 H, J = 16.1 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 3.89 (s, 3 H), 1.63 (s, 6 H), 1.33 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 172.8, 171.2, 166.4, 149.1, 137.3, 131.1, 127.4, 127.1, 126.5, 122.6, 120.4, 60.5, 52.9, 50.1, 22.9, 14.2; HRMS *m/e* for $C_{17}H_{20}O_6$: calcd 320.1260. Found: 320.1257.

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.25. Found: C, 63.69; H, 6.23.

Ethyl (*E*)-3-(2-Hydroxy-1-naphthyl)propenoate (12). A mixture of 5.00 g (29.1 mmol) of 2-hydroxy-1-naphthaldehyde and 20.3 g (58.2 mmol) of ethyl (triphenylphosphoranylidene)acetate in 300 mL of benzene was heated under reflux for 12 h. The reaction was cooled and concentrated to afford a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the

filtrate afforded the crude hydroxy ester as a yellow oil. Final purification by flash chromatograhy on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 4.43 g (18.3 mmol, 63%) of the hydroxy ester as a viscous oil. IR (thin film) 3325, 1678, 1619, 1597, 1509, 1378, 975 cm^{-1}; ^1H NMR δ 8.35 (d, 1 H, *J* = 16.2 Hz), 8.05 (d, 1 H, *J* = 8.6 Hz), 7.76 (t, 2 H, *J* = 8.1 Hz), 7.52 (t, 1 H, *J* = 8.2 Hz), 7.37 (t, 1 H, *J* = 8.2 Hz), 7.17 (d, 1 H, *J* = 8.9 Hz), 6.84 (d, 1 H, *J* = 16.2 Hz), 6.80 (s, 1 H), 4.36 (q, 2 H, *J* = 7.2 Hz), 1.40 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 168.0, 153.3, 138.5, 132.7, 131.6, 128.9, 128.6, 127.4, 123.8, 123.2, 122.9, 118.1, 113.8, 60.9, 14.4; HRMS *m/e* for $C_{15}H_{14}O_3$: calcd 242.0943. Found: 242.0935.

(*E*)-2-(2-Ethoxycarbonylethenyl)-1-Naphthyl Methyl Dimethylpropanedioate. (13). To a stirred 0 °C solution of 4.00 g (16.5 mmol) of **12**, 2.50 g (3.44 mL, 24.8 mmol) of Et_3N and 0.15 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 2.88 g (17.5 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the major band gave 4.29 g (11.6 mmol, 70%) of the triester as a yellow oil. IR (thin film) 1770, 1743, 1722, 1648, 1392, 1369, 989 cm^{-1}; ^1H NMR δ 8.09 (d, 1 H, *J* = 7.6 Hz), 8.03 (d, 1 H, *J* = 16.4 Hz), 7.85 (m, 2 H), 7.54 (m, 2 H), 7.19 (d, 1 H, *J* = 8.9 Hz), 6.38 (d, 1 H, *J* = 16.4 Hz), 4.31 (q, 2 H, *J* = 7.1 Hz), 3.85 (s, 3 H), 1.62 (s, 6 H), 1.36 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 172.8, 171.1, 166.2, 146.1, 137.0, 131.7, 130.5, 128.5, 127.3, 126.2, 126.1, 126.0, 124.5, 123.8, 120.9, 60.6, 52.8, 50.1, 22.8, 22.0, 14.2; HRMS *m/e* for $C_{21}H_{22}O_6$: calcd 370.1416. Found: 370.1408.

Ethyl (*E*)-3-(2-Hydroxy-4-methoxyphenyl) propenoate. (15). A mixture of 5.00 g (32.9 mmol) of 2-hydroxy-4-methoxybenzaldehyde and 22.9 g (65.8

mmol) of ethyl (triphenylphosphoranylidene)acetate in 300 mL of benzene was heated under reflux for 12 h. The reaction was cooled and concentrated to afford a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude hydroxy ester as a yellow oil. Final purification by flash chromatography on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 5.25 g (25.0 mmol, 76%) of the hydroxy ester as a viscous oil. IR (thin film) 3340, 2842, 1678, 1619, 1590, 1377, 981 cm^{-1}; ^1H NMR δ 8.01 (d, 1 H, J = 15.9 Hz), 7.63 (s, 1 H), 7.38 (d, 1 H, J = 8.6 Hz), 6.55 (d, 2 H, J = 15.9 Hz), 6.45 (m, 1 H), 4.28 (q, 2 H, J = 7.1 Hz), 3.78 (s, 3 H), 1.34 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 169.2, 162.5, 157.3, 140.9, 130.5, 115.2, 115.0, 106.8, 101.8, 60.6, 55.3, 14.3; HRMS *m/e* for $C_{12}H_{14}O_4$: calcd 210.0892. Found: 210.0890.

(*E*)-2-(2-Ethoxycarbonylethenyl)-5-methoxyphenyl Methyl Dimethylpropanedioate (16). To a stirred 0 °C solution of 4.75 g (22.6 mmol) of **15**, 3.43 g (4.72 mL, 33.9 mmol) of Et_3N and 0.15 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 4.00 g (24.3 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the ma*J*or band gave 6.16 g (17.6 mmol, 78%) of the triester as a yellow oil. IR (thin film) 2843, 1767, 1743, 1722, 1634, 1612, 1509, 1392, 1370, 982 cm^{-1}; ^1H NMR δ 7.69 (d, 1 H, J = 15.9 Hz), 7.59 (d, 1 H, J = 8.9 Hz), 6.81 (dd, 1 H, J = 8.9, 2.5 Hz), 6.59 (d, 1 H, J = 2.5 Hz), 6.32 (d, 1 H, J = 15.9 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 3.89 (s, 3 H), 3.81 (s, 3 H), 1.64 (s, 6 H), 1.32 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 172.6,

170.9, 166.7, 161.8, 150.2, 137.1, 127.6, 119.7, 117.8, 113.6, 107.1, 60.2, 55.5, 55.3, 50.0, 22.8, 14.2; HRMS *m/e* for $C_{18}H_{22}O_7$: calcd 350.1365. Found: 350.1369.

Tetrahydro-2-(3-methylphenoxy)-2*H*-pyran (17): To a solution of 21.6 g (0.20 mol) of 3-methylphenol and 33.6 g (0.40 mol) of dihydropyran in 100 mL of $CHCl_3$ was added 5 mg of *p*-TsOH. The solution became warm and stirring was continued for 2.5 h as the reaction returned to rt. The $CHCl_3$ was removed under vacuum and the crude product was diluted with ether, washed with 10% NaOH (3x) and NaCl (1x), dried (Na_2SO_4), and concentrated under vacuum. The resulting oil was vacuum distilled from NaOH pellets (*ca.* 1 g) to give 34.3 g (0.18 mol, 89.5%) of **10** as a colorless oil, bp 74-75 °C (0.5 mm Hg); IR (thin film) 3040, 1612, 1590, 1502, 1370, 777, 696 cm^{-1}; ^1H NMR δ 7.14 (t, 1 H, *J* = 7.6 Hz), 6.87 (s, 1 H), 6.86 (d, 1 H, *J* = 7.6 Hz), 6.78 (d, 1 H, *J* = 7.6 Hz), 5.39 (t, 1 H, *J* = 2.9 Hz), 3.91 (td, 1 H, *J* = 10.4, 2.9 Hz), 3.59 (dt, 1 H, *J* = 10.4, 4.1 Hz), 2.31 (s, 3 H), 2.00 (m, 1 H), 1.84 (m, 2 H), 1.71-1.53 (complex, 3 H); ^{13}C NMR δ 157.0, 139.3, 129.0, 122.3, 117.1, 113.3, 96.1, 61.9, 30.3, 25.2, 21.4, 18.7; HRMS: *m/e* for $C_{12}H_{16}O_2$: calcd 192.1150. Found: 192.1145.

Ethyl (*E*)-3-(2-hydroxy-4-methylphenyl)propenoate (21). To 16.3 mL of 1.35 M *n*-BuLi in hexanes (22.0 mmol) at 0 °C was added 2.55 g (3.31 mL, 22.0 mmol) of TMEDA dropwise with stirring. The solution was stirred for 30 min at 0 °C and a solution of 3.84 g (20.0 mmol) of **17** in 3.0 mL of hexanes was added dropwise during 30 min. The reaction was stirred at 0 °C for 2.5 h during which time a white precipitate formed. The slurry was transferred by cannula under N_2 pressure to a 0 °C solution of 5.12 g (5.42 mL, 70.0 mmol) of DMF in 15 mL of toluene. The reaction was warmed to rt and stirred for 6 h, then transferred to a separatory funnel containing 100 mL of ice-cold 1 M HCl, and extracted with ether (2x). The combined ether extracts were washed with NaCl, dried (Na_2SO_4), and concentrated under vacuum.

To the resulting yellow oil was added 100 mL of benzene and 10.0 g (28.7 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 6

h, then cooled and concentrated to afford a yellow semisolid mass. The residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 1 L of 15% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate gave the THP-protected *o*-hydroxycinnamate ester **20** as a light yellow oil.

The ester was dissolved in 100 mL of absolute EtOH, 0.5 g of *p*-TsOH was added, and the solution was stirred at rt for 12 h. The EtOH was removed under vacuum, ether (*ca.* 25 mL) and silica gel (*ca.* 5 g) were added, and the mixture was concentrated to dryness. The silica gel-product mixture was loaded onto a 30-cm x 2.5-cm plug of silica gel and eluted with increasing concentrations of ether in hexanes. Concentration of the ma*J*or band gave the ethyl (*E*)-3-(2-hydroxy-4-methylphenyl)propenoate (**21**) as an off-white solid. The product was triturated with hexanes and filtered to give 2.14 g (10.4 mmol, 52%) of **21** as a white powder, mp 95-96 °C; IR (thin film) 3216, 1685, 1624, 1612, 1370 cm^{-1}; ^1H NMR δ 8.04 (d, 1 H, *J* = 16.2 Hz), 7.34 (d, 1 H, *J* = 7.7 Hz), 7.32 (bs, 1 H), 6.70 (d, 1 H, *J* = 7.7 Hz), 6.69 (s, 1 H), 6.63 (d, 1 H, *J* = 16.2 Hz), 4.29 (q, 2 H, *J* = 7.0 Hz), 2.28 (s, 3 H), 1.35 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 168.8, 155.5, 142.3, 140.8, 129.1, 121.6, 119.0, 117.2, 117.0, 60.6, 21.4, 14.3; HRMS *m/e* for $C_{12}H_{14}O_3$: calcd 206.0943. Found: 206.0939.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.87; H, 6.79.

(*E*)-2-(2-Ethoxycarbonylethenyl)-5-methylphenyl Methyl Dimethylpropanedioate (22). To a stirred 0 °C solution of 2.06 g (10.0 mmol) of **21**, 1.52 g (2.09 mL, 15.0 mmol) of Et_3N and 0.10 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 2.00 g (12.2 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes.

Concentration of the major band gave 2.64 g (7.9 mmol, 79%) of the triester as a light yellow solid, mp 38-40 °C. IR (thin film) 1772, 1751, 1722, 1641, 1612, 1509, 1392, 1370, 982 cm^{-1}; ^1H NMR δ 7.72 (d, 1 H, *J* = 16.1 Hz), 7.54 (d, 1 H, *J* = 7.9 Hz), 7.07 (dd, 1 H, *J* = 8.0, 1.8 Hz), 6.88 (d, 1 H, *J* = 1.8 Hz), 6.39 (d, 1 H, *J* = 16.1 Hz), 4.24 (q, 2 H, *J* = 7.2 Hz), 3.89 (s, 3 H), 2.36 (s, 3 H), 1.63 (s, 6 H), 1.32 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 172.7, 171.2, 166.6, 149.0, 142.0, 137.2, 127.4, 126.8, 124.4, 122.9, 119.1, 60.3, 52.8, 50.0, 22.8, 21.2, 14.2; HRMS *m/e* for $C_{18}H_{22}O_6$: calcd 334.1416. Found: 334.1411.

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.67; H, 6.59 Found: C, 64.75; H, 6.63.

Representative Procedure for Dealkoxycarbonylation-Michael Addition. Ethyl 3,4-Dihydro-3,3-dimethylcoumarin-4-acetate (23). A solution of 530 mg (4.00 mmol) of dry LiI and 320 mg (1.00 mmol) of **10** in 8.5 mL of DMEU was heated in an oil bath at 100 °C (± 2 °C). After 48 h, GC analysis indicated that the reaction was complete. The crude reaction mixture was cooled, added to saturated NH_4Cl, and extracted with ether (3x). The combined organic layers were washed with NH_4Cl (2x), 5% Na_2SO_4 (1x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by PTLC, eluting with increasing concentrations of ether in hexanes to afford 162 mg (0.62 mmol, 62%) of the dihydrocoumarin product as a light yellow oil. IR (thin film) 1767, 1733, 1616, 1593, 1490, 1395, 1377, 761 cm^{-1}; ^1H NMR δ 7.27 (t, 1 H, *J* = 7.8 Hz), 7.20 (d, 1 H, *J* = 7.6 Hz), 7.08 (t, 1 H, *J* = 7.5 Hz), 7.02 (d, 1 H, *J* = 8.0 Hz), 4.05 (m, 2 H), 3.19 (dd, 1 H, *J* = 9.4, 4.9 Hz), 2.75 (dd, 1 H, *J* = 15.4, 4.9 Hz), 2.35 (dd, 1 H, *J* = 15.4, 9.4 Hz), 1.37 (s, 3 H), 1.21 (s, 3 H), 1.16 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 173.0, 171.4, 150.5, 128.7 (2), 125.2, 124.4, 116.4, 60.8, 43.7, 40.7, 37.1, 25.2, 21.7, 14.0; HRMS *m/e* for $C_{15}H_{18}O_4$ calcd 262.1205, found 262.1204.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.62; H, 6.86.

Ethyl 5,6-Benzo-3,4-dihydro-3,3-dimethylcoumarin-4-acetate (24). The preparation of this compound was accomplished by heating 370 mg (1.00 mmol) of **13** with 530 mg (4.00 mmol) of dry LiI in 8.34 mL of DMEU for 48 h at 100 °C. The yield, after PTLC, was 125 mg (0.40 mmol, 40%) of the dihydrocoumarin product as a yellow oil. IR (thin film) 1770, 1732, 1627, 1516, 816, 750 cm^{-1}; ^1H NMR δ 8.00 (d, 1 H, J = 8.5 Hz), 7.85 (d, 1 H, J = 8.2 Hz), 7.78 (d, 1 H, J = 8.9 Hz), 7.59 (t, 1 H, J = 7.1 Hz), 7.47 (t, 1 H, J = 7.1 Hz), 7.21 (d, 1 H, J = 8.9 Hz), 4.04 (m, 2 H), 3.95 (m, 1 H), 2.72 (dd, 1 H, J = 16.1, 7.8 Hz), 2.49 (dd, 1 H, J = 16.1, 4.3 Hz), 1.47 (s, 3 H), 1.24 (s, 3 H), 1.12 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 172.8, 171.7, 148.1, 131.0, 130.6, 129.4, 128.8, 127.4, 125.0, 122.5, 118.5, 116.8, 60.9, 41.0, 40.0, 36.9, 25.6, 21.6, 13.8; HRMS *m/e* for $C_{19}H_{20}O_4$: calcd 312.1361. Found: 312.1365.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.26; H, 6.49.

Ethyl 3,4-dihydro-7-methoxy-3,3-dimethylcoumarin-4-acetate (25). The preparation of this compound was accomplished by heating 350 mg (1.00 mmol) of **16** with 530 mg (4.00 mmol) of dry LiI in 8.5 mL of DMEU for 48 h at 100 °C. The yield, after PTLC, was 134 mg (0.46 mmol, 46%) of the dihydrocoumarin product as a yellow oil. IR (thin film) 2840, 1767, 1733, 1626, 1590, 1509 cm^{-1}; ^1H NMR δ 7.10 (d, 1 H, J = 8.4 Hz), 6.64 (dd, 1 H, J = 8.4, 2.6 Hz), 6.58 (d, 1 H, J = 2.6 Hz), 4.06 (m, 2 H), 3.79 (s, 3 H), 3.12 (dd, 1 H, J = 9.6, 4.8 Hz), 2.72 (dd, 1 H, J = 15.3, 4.8 Hz), 2.31 (dd, 1 H, J = 15.3, 9.6 Hz), 1.36 (s, 3 H), 1.21 (s, 3 H), 1.17 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 172.9, 171.4, 159.8, 151.2, 129.2, 117.0, 110.2, 101.9, 60.6, 55.3, 43.0, 40.7, 37.3, 25.2, 21.7, 14.0; HRMS *m/e* for $C_{16}H_{20}O_5$: calcd 292.1310. Found: 292.1304.

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.75; H, 6.85. Found: C, 65.93; H, 6.91.

Ethyl 3,4-Dihydro-3,3,7-trimethylcoumarin-4-acetate (26). The preparation of this compound was accomplished by heating 334 mg (1.00 mmol) of **22** with 530 mg (4.00 mmol) of dry LiI in 8.5 mL of DMEU for 48 h at 100 °C. The yield,

after PTLC, was 102 mg (0.37 mmol, 37%) of the dihydrocoumarin product as a yellow oil. IR (thin film) 1765, 1734, 1626, 1580, 1504, 1390, 1373, 805 cm^{-1}; ^1H NMR δ 7.07 (d, 1 H, *J* = 7.7 Hz), 6.89 (d, 1 H, *J* = 7.7 Hz), 6.84 (s, 1 H), 4.06 (m, 2 H), 3.14 (dd, 1 H, *J* = 9.5, 4.8 Hz), 2.72 (dd, 1 H, *J* = 15.4, 4.8 Hz), 2.33 (s, 3 H), 2.32 (dd, 1 H, *J* = 15.4, 9.5 Hz), 1.36 (s, 3 H), 1.20 (s, 3 H), 1.17 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 173.2, 171.5, 150.3, 138.9, 128.3, 125.1, 122.1, 116.8, 60.7, 43.4, 40.8, 37.3, 25.3, 21.8, 21.1, 14.0; HRMS *m/e* for $C_{16}H_{20}O_4$: calcd 276.1361. Found: 276.1356.

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.57; H, 7.25. Found: C, 69.66; H, 7.28.

Methyl 2-(*N*-(3-Butenyl)carbamoyl)-2-methylpropanoate (34). To a stirred 0 °C solution of 3.00 g (42.2 mmol) of 3-butenylamine, 6.40 g (8.81 mL, 63.3 mmol) of Et_3N and 0.10 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 11.2 g (68.0 mmol) of methyl dimethylmalonyl chloride in 25 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the major band gave 7.48 g (37.6 mmol, 89%) of the diester **34** as a yellow oil. IR (thin film) 3360, 1750, 1660, 1535, 1391, 1370, 995, 916 cm^{-1}; ^1H NMR δ 6.39 (bs, 1 H), 5.76 (m, 1 H), 5.11 (d, 1 H, *J* = 2.4 Hz), 5.07 (d, 1 H, *J* = 1.7 Hz), 3.73 (s, 3 H), 3.32 (q, 2 H, *J* = 6.7 Hz), 2.26 (m, 2 H), 1.44 (s, 6 H); ^{13}C NMR δ 175.4, 171.6, 135.2, 117.2, 52.6, 49.8, 38.6, 33.6, 23.6; HRMS *m/e* for $C_{10}H_{17}NO_3$: calcd 199.1208. Found: 199.1205.

Methyl 2-(*N*-(4-Ethoxycarbonyl-3-butenyl)carbamoyl)-2-methylpropanoate (36). A solution of 5.00 g (25.1 mmol) of **34** in 150 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 5.31 g (6.28 mL, 85.6 mmol) of dimethyl sulfide, warmed to rt,

stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 13.9 g (40.2 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 12 h, then cooled to rt and concentrated under vacuum to give a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatograhy on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.74 g (13.8 mmol, 55%) of **36** as a yellow oil. IR (thin film) 3355, 1726, 1657, 1538, 1390, 1369, 978 cm^{-1}; ^1H NMR δ 6.87 (dt, 1 H, *J* = 15.8, 7.1 Hz), 6.51 (bs, 1 H), 5.86 (dt, 1 H, *J* = 15.8, 1.3 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.73 (s, 3 H), 3.40 (q, 2 H, *J* = 5.9 Hz), 2.43 (m, 2 H), 1.44 (s, 6 H), 1.29 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 175.4, 171.8, 166.1, 144.9, 123.5, 60.3, 52.7, 49.8, 38.1, 32.0, 23.6, 14.2; HRMS *m/e* for $C_{13}H_{21}NO_5$: calcd 271.1419. Found: 271.1423.

***N*-(3-Butenyl)benzamide (37).** To a stirred 0 °C solution of 4.25 g (59.6 mmol) of 3-butenylamine, 9.08 g (12.5 mL, 89.9 mmol) of Et_3N, and 0.20 g of DMAP in 75 mL of CH_2Cl_2 was added a solution of 9.00 g (64.0 mmol) of benzoyl chloride in 20 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the ma*J*or band gave 6.77 g (38.7 mmol, 65%) of the amide as a yellow oil. IR (thin film) 3317, 3077, 1640, 1534, 996, 921 cm^{-1}; ^1H NMR δ 7.78 (d, 2 H, *J* = 8.4 Hz), 7.42 (m, 1 H), 7.35 (m, 2 H), 7.08 (bs, 1 H), 5.81 (ddt, 1 H, *J* = 17.1, 10.2, 6.9 Hz), 5.08 (d, 1 H, *J* = 17.1 Hz), 5.05 (d, 1 H, *J* = 10.2 Hz), 3.46 (q, 2 H, *J* = 6.9 Hz), 2.33 (m, 2 H); ^{13}C NMR δ 167.6, 135.1, 134.5, 131.1,

128.2, 126.8, 116.8, 38.8, 33.5; HRMS *m/e* for $C_{11}H_{13}NO$: calcd 175.1034. Found: 175.1034.

***N*-Benzyl-3-butenamine (38).** This compound was prepared using an adaptation of the procedure reported by Heathcock and co-workers[101] for the preparation of *N*-benzyl-4-pentenylamine. To a solution of 5.00 g (28.6 mmol) of *N*-(3-butenyl)benzamide in 80 mL of CH_2Cl_2 at -78 °C was added 114.4 mL (114.4 mmol) of 1.0 M DIBAL in toluene dropwise over 1 h. The resulting solution was warmed to rt and stirred for 1 h, then heated to 50 °C for 90 min. The mixture was cooled to rt and cautiously quenched with 25 mL of water, poured into 1 L of 15% NaOH-sodium potassium tartrate (1:1), and extracted with ether (2x). The organic layers were combined, dried (K_2CO_3), and concentrated under vacuum. The crude product was vacuum distilled through a 15-cm Vigreux column to afford 4.19 g (26.0 mmol, 91%) of the amine as a colorless oil, bp 50-52 °C (0.5 mm Hg). IR (thin film) 3311, 3079, 1640, 999, 921, 728, 704 cm^{-1}; ^1H NMR δ 7.30-7.18 (complex, 5 H), 5.75 (ddt, 1 H, *J* = 17.3, 10.1, 6.9 Hz), 5.07 (d, 1 H, *J* = 17.3 Hz), 5.01 (d, 1 H, *J* = 10.1 Hz), 3.75 (s, 2 H), 2.67 (t, 2 H, *J* = 6.9 Hz), 2.25 (m, 2 H), 1.62 (bs, 1 H); ^{13}C NMR δ 140.4, 136.5, 128.5, 128.2, 127.0, 116.4, 53.9, 48.3, 34.3; HRMS *m/e* for $C_{11}H_{15}N$: calcd 161.1242. Found: 161.1236.

Methyl 2-(*N*-Benzyl-*N*-(3-butenyl)carbamoyl)-2-methylpropanoate (39). To a stirred 0 °C solution of 4.15 g (25.7 mmol) of *N*-benzyl-3-butenamine, 3.91 g (5.38 mL, 38.7 mmol) of Et_3N and 0.15 g of DMAP in 100 mL of CH_2Cl_2 was added a solution of 4.77 g (29.0 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by chromatography on an 80-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes.

The major band yielded 5.49 g (19.0 mmol, 74%) of the amido ester as a light yellow oil. IR (thin film) 3070, 1734, 1645, 1394, 1372, 998, 918, 730, 700 cm^{-1}; ^1H NMR (2 rotamers) δ 7.34-7.10 (complex, 5 H), 5.72 and 5.63 (2 m, 1 H), 5.02 (m, 2 H), 4.67 and 4.40 (2 s, 2 H), 3.75 and 3.41 (2 s, 3 H), 3.36 and 3.08 (2 m, 2 H), 2.28 (m, 2 H), 1.49 and 1.47 (2 s, 6 H); ^{13}C NMR (2 rotamers) δ 175.3, 171.9, 137.1, 135.9, 135.5, 133.8, 128.6, 128.5, 127.4, 127.3, 126.6, 117.3, 116.8, 52.3, 52.1, 50.7, 49.0, 47.7, 45.4, 31.8, 31.1, 24.5, 22.7, 22.0; HRMS *m/e* for $C_{17}H_{23}NO_3$: calcd 289.1715. Found: 289.1711.

Methyl (*E*)-2-(*N*-Benzyl-*N*-(4-ethoxycarbonyl-3-butenyl)carbamoyl)-2-methylpropanoate (40). A solution of 5.38 g (18.6 mmol) of methyl 2-(*N*-benzyl-*N*-(3-butenyl)carbamoyl)-2-methylpropanoate in 200 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 5.00 g (5.91 mL, 80.6 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 10.4 g (29.8 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 12 h, then cooled to rt and concentrated under vacuum to give a tan semisolid mass. The residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatography on a 80-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.89 g (10.7 mmol, 58%) of the amido diester as a light yellow oil. IR (thin film) 1727, 1647, 1392, 1371, 972, 739, 704 cm^{-1}; ^1H NMR (2 rotamers) δ 7.36-7.12 (complex, 5 H), 6.84 and 6.74 (2 m, 1 H), 5.81 (d, 1 H, J = 15.5 Hz), 4.68 and 4.38 (2 s, 2 H), 4.18 (q, 2 H, J = 7.1 Hz), 3.73 and 3.49 (2 s, 3 H), 3.40 and 3.18 (2 m, 2 H), 2.44 (m, 2 H), 1.49 and 1.48 (2 s, 6 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (2 rotamers) δ 172.0, 171.7, 166.2, 145.4, 143.5, 138.1, 135.5, 128.7, 128.6, 127.7, 127.6, 127.4, 127.3, 126.7, 123.2, 60.1, 52.3 (2), 51.0,

49.8, 49.0, 47.8, 44.8, 44.7, 43.7, 29.5, 24.5, 23.6, 14.1; HRMS *m/e* for $C_{20}H_{27}NO_5$: calcd 361.1926. Found: 361.1914.

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.48; H, 7.48. Found: C, 66.27; H, 7.44.

***N*-Phenyl-*N*-butenylamine (42).** A solution of 18.63 g (200 mmol) of aniline and 2.70 g (20 mmol) of 4-bromo-1-butene was stirred at 65 °C for 24 h. The reaction was cooled and poured into 1 M NaOH and extracted with ether (3x). The combined extracts were washed with 1 M NaOH (2x) and NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum. The crude product was distilled to yield 2.45 g (16.7 mmol, 83%) of clear colorless oil, bp 47-48 °C (0.5 mm Hg). IR (thin film) 3416, 3082, 3061, 3025, 1644, 1603, 1509, 997, 919, 747, 698 cm^{-1}; ^1H NMR δ 7.15 (t, 2 H, *J* = 8.1 Hz), 6.70 (t, 1 H, *J* = 8.1 Hz), 6.59 (d, 2 H, *J* = 8.3 Hz), 5.80 (ddt, 1 H, *J* = 17.1, 10.3, 6.8 Hz), 5.12 (d, 1 H, *J* = 17.1 Hz), 5.09 (d, 1 H, *J* = 10.3 Hz), 3.61 (bs, 1 H), 3.14 (t, 2 H, *J* = 6.6 Hz), 2.34 (m, 2 H); ^{13}C NMR δ 148.1, 135.7, 129.1, 117.2, 116.9, 112.8, 42.7, 33.5; HRMS *m/e* for $C_{10}H_{13}N$: calcd 147.1048. Found: 147.1049.

Methyl 2-(*N*-(3-Butenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (43). To a stirred 0 °C solution of 2.00 g (13.6 mmol) of **42**, 2.06 g (2.84 mL, 20.4 mmol) of Et_3N and 0.10 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 2.68 g (16.3 mmol) of methyl dimethylmalonyl chloride in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the major band gave 2.64 g (7.9 mmol, 79%) of **27** as a yellow solid. IR (thin film) 1734, 1650, 1596, 1488, 1389, 990, 913, 767, 706 cm^{-1}; ^1H NMR δ 7.37 (m, 3 H), 7.16 (m, 2 H), 5.76 (ddt, 1 H, *J* = 16.8, 10.3, 7.0 Hz), 5.06 (d, 1 H, *J* = 16.8 Hz), 5.02 (d, 1 H, *J* = 10.3 Hz), 3.71 (t, 2 H, *J* = 7.3 Hz), 3.45 (bs, 3 H), 2.29 (q, 2 H, *J* = 7.3 Hz),

1.34 (s, 6 H); ^{13}C NMR δ 174.1, 171.4, 140.7, 135.1, 130.3, 129.0, 128.5, 116.6, 52.5, 51.9, 50.1, 31.8, 25.4; HRMS *m/e* for $C_{16}H_{21}NO_3$: calcd 275.1521. Found: 275.1509.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.64. Found: C, 69.91; H, 7.76.

Methyl (*E*)-2-(*N*-(4-Ethoxycarbonyl-3-butenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (44). A solution of 3.00 g (10.9 mmol) of **43** in 150 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 2.31 g (2.73 mL, 37.2 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 6.02 g (17.4 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 12 h, then cooled to rt and concentrated under vacuum to give a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatograhy on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 2.12 g (6.11 mmol, 56%) of **44** as a yellow oil. IR (thin film) 1740, 1722, 1652, 1595, 1495, 1394 cm^{-1}; ^{1}H NMR δ 7.41-7.35 (complex, 3 H), 7.15 (d, 2 H, *J* = 7.9 Hz), 6.87 (dt, 1 H, *J* = 15.8, 7.3 Hz), 5.85 (d, 1 H, *J* = 15.8 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz), 3.77 (t, 2 H, *J* = 7.3 Hz), 3.46 (s, 3 H), 2.48 (q, 2 H, *J* = 7.0 Hz), 1.33 (s, 6 H), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 173.9, 171.4, 166.1, 145.0, 140.5, 130.0, 129.1, 128.7, 123.0, 60.1, 51.8, 50.3, 50.0, 30.1, 25.2, 14.1; HRMS *m/e* for $C_{19}H_{25}NO_5$: calcd 347.1732. Found: 347.1720.

Anal. Calcd for $C_{19}H_{25}NO_5$: C, 67.51; H, 7.20. Found: C, 65.83; H, 7.27.

2-Aminobenzaldehyde (46). This compound was prepared in 56% yield using the procedure of Wood and co-workers.[102] The physical and spectral properties matched those reported.

Ethyl (*E*)-3-(2-Aminophenyl)propenoate (47). A mixture of 3.64 g (30.0 mmol) of 2-aminobenzaldehyde and 10.8 g (31.0 mmol) of ethyl (triphenylphosphoranylidene)acetate in 200 mL of benzene was heated under reflux for 12 h. The reaction was cooled and concentrated to afford a brown semisolid mass. This residue was loaded onto a 10-cm x 5-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude amino ester as a dark yellow oil which crystallized on standing. Final purification by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.78 g (19.8 mmol, 66%) of the amino ester as a yellow solid, mp 68-69 °C. IR ($CHCl_3$) 3469, 3370, 3233, 1693, 1622, 1602, 1488, 1374, 756 cm^{-1}; ^1H NMR δ 7.82 (d, 1 H, J = 15.7 Hz), 7.37 (d, 1 H, J = 7.7 Hz), 7.16 (t, 1 H, J = 7.5 Hz), 6.75 (t, 1 H, J = 7.5 Hz), 6.68 (d, 1 H, J = 7.7 Hz), 6.34 (d, 1 H, J = 15.7 Hz), 4.25 (q, 2 H, J = 7.2 Hz), 4.01 (br s, 2 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 167.3, 145.6, 140.0, 131.2, 128.0, 119.8, 118.8, 118.0, 116.6, 60.4, 14.2; HRMS *m/e* for $C_{11}H_{13}NO_2$: calcd 191.0983. Found: 191.0979.

Methyl (*E*)-2-(*N*-(2-(2-Ethoxycarbonylethenyl)phenyl)carbamoyl)-2-methylpropanoate (48). To a stirred 0 °C solution of 2.50 g (13.1 mmol) of ethyl (*E*)-3-(2-aminophenyl)propenoate, 1.98 g (2.73 mL, 19.6 mmol) of Et_3N, and 0.12 g of DMAP in 30 mL of CH_2Cl_2 was added a solution of 2.46 g (15.0 mmol) of methyl dimethylmalonyl chloride in 10 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 40-cm x 2-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the ma*J*or band gave 3.26 g (10.2 mmol, 78%) of the amido diester as a yellow oil. IR (thin film) 3307, 1741, 1715, 1689, 1636, 1394, 1372, 765 cm^{-1}; ^1H NMR δ 8.68 (bs, 1 H), 7.80 (d, 1 H, J =

15.8 Hz), 7.76 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 7.8 Hz), 7.39 (t, 1 H, J = 7.8 Hz), 7.21 (t, 1 H, J = 7.7 Hz), 6.40 (d, 1 H, J = 15.8 Hz), 4.27 (q, 2 H, J = 7.1 Hz), 3.87 (s, 3 H), 1.60 (s, 6 H), 1.34 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 175.6, 170.3, 166.5, 138.9, 135.7, 130.5, 128.0, 126.9, 125.9, 124.9, 120.6, 60.4, 53.0, 50.3, 23.8, 14.1; HRMS *m/e* for $C_{17}H_{21}NO_5$: calcd 319.1448. Found: 319.1448.

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58. Found: C, 63.82; H, 6.55.

***N*-Allylacetanilide (50).** To a solution of 0.33 g (8.1 mmol) of NaH in 5 mL of DMF at rt was added 1.00 g (7.4 mmol) of acetanilide in 2 mL of DMF dropwise over 30 min. A solution of 1.16 g (9.62 mmol) of allyl bromide was then added dropwise at rt over 30 min. GC analysis indicated no starting material after 2 h of stirring. The reaction was poured into 50 mL of NH_4Cl and extracted with ether (3x). The combined extracts were washed with 1 M HCl (2x), H_2O (2x), NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum to yield 0.95 g of yellow oil. The crude product was used without further purification. IR (thin film) 1662, 1604, 1502, 1399, 989, 923 cm $^{-1}$; ^{1}H NMR δ 7.40 (t, 2 H, J = 7.0 Hz), 7.34 (d, 1 H, J = 8.1 Hz), 7.17 (d, 2 H, J = 8.1 Hz), 5.88 (ddt, 1 H, J = 17.2, 10.6, 6.3 Hz), 5.10 (d, 1 H, J = 10.6 Hz), 5.06 (d, 1 H, J = 17.2 Hz), 4.30 (d, 2 H, J = 6.3 Hz), 1.86 (s, 3 H); ^{13}C NMR δ 169.8, 142.8, 132.9, 129.3, 127.8, 127.6, 117.5, 51.8, 22.4; HRMS *m/e* for $C_{11}H_{13}NO$: calcd 175.2298. Found: 175.2289.

***N*-Allylaniline (51).** A solution of 13.47 g (77.0 mmol) of **50** in 30 mL of 10% HCl (xs) was placed in an oil bath and allowed to stir at reflux for 24 h. The reaction mixture was cooled and basified using Na_2CO_3, then extracted with ether (3x). The combined extracts were washed with $NaHCO_3$ (1x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum. The crude product was distilled to yield 7.55 g (56.8 mmol, 74%) of a clear colorless liquid, bp 45 °C (0.5 mm Hg). IR (thin film) 3413, 1603, 1504, 1432, 997, 924 cm $^{-1}$; ^{1}H NMR δ 7.17 (t, 2 H, J = 7.5 Hz), 6.70 (t, 1 H, J = 7.3 Hz), 6.61 (d, 2 H, J = 7.8 Hz), 5.94 (ddt, 1 H, J = 17.2, 10.3, 5.5 Hz), 5.27 (d, 1

H, J = 17.2 Hz), 5.16 (d, 1 H, J = 10.3 Hz), 3.75 (dt, 3 H, J = 5.5, 1.5 Hz); ^{13}C NMR δ 148.0, 135.4, 129.2, 117.4, 116.1, 112.9, 46.4; HRMS *m/e* for $C_9H_{11}N$: calcd 133.0892,. Found: 133.0890.

Methyl 2-(*N*-Phenyl-*N*-(2-propenyl)carbamoyl)-2-methylpropanoate (52). To a stirred 0 °C solution of 4.00 g (30.1 mmol) of *N*-allylaniline, 4.56 g (6.28 mL, 45.1 mmol) of Et_3N, and 0.15 g of DMAP in 40 mL of CH_2Cl_2 was added a solution of 5.84 g (35.5 mmol) of methyl dimethylmalonyl chloride in 20 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the maJor band gave 5.52 g (21.1 mmol, 70%) of the amido diester as a yellow oil. IR (thin film) 1734, 1676, 1602, 1504, 1392, 1374, 754, 989, 913, 698 cm^{-1}; ^{1}H NMR δ 7.36 (m, 3 H), 7.14 (m, 2 H), 5.87 (ddt, 1 H, J = 17.1, 10.2, 5.0 Hz), 5.12 (d, 1 H, J = 10.2 Hz), 5.06 (d, 1 H, J = 17.1 Hz), 4.23 (d, 2 H, J = 5.0 Hz), 3.46 (s, 3 H), 1.36 (s, 6 H); ^{13}C NMR δ 174.1, 171.4, 140.7, 132.7, 130.2, 128.9, 128.6, 117.9, 55.0, 51.9, 50.0, 25.3; HRMS *m/e* for $C_{15}H_{19}NO_3$: calcd 261.1402. Found: 261.1403.

Methyl (*E*)-2-(*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (53). A solution of 5.11 g (19.6 mmol) of methyl 2-(*N*-phenyl-*N*-(2-propenyl)carbamoyl)-2-methylpropanoate in 200 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 4.50 g (5.32 mL, 72.5 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 10.9 g (31.4 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 12 h, then cooled to rt, and concentrated under vacuum to give a tan semisolid mass. The residue was loaded onto a 15-cm x 5-cm plug of

silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatography on a 50-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.59 g (10.8 mmol, 55%) of the amido diester as a yellow oil. IR (thin film) 1738, 1713, 1680, 1604, 1502, 1390, 1372, 980, 751, 696 cm^{-1}; ^1H NMR δ 7.38 (m, 3 H), 7.15 (m, 2 H), 6.91 (dt, 1 H, *J* = 15.7, 5.8 Hz), 5.89 (d, 1 H, *J* = 15.7 Hz), 4.38 (dd, 2 H, *J* = 5.8, 1.6 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.48 (s, 3 H), 1.36 (s, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 174.0, 171.6, 166.0, 142.2, 140.7, 129.9, 129.3, 128.9, 123.2, 60.4, 53.3, 52.0, 50.0, 25.3, 14.1; HRMS *m/e* for $C_{18}H_{23}NO_5$: calcd 333.1613. Found: 333.1605.

Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.91. Found: C, 64.98; H, 6.94.

Representative Procedure for Dealkoxycarbonylation-Michael Addition. Ethyl 3,3-Dimethyl-1-phenyl-2-piperidinone-4-acetate (54). A solution of 530 mg (4.00 mmol) of dry LiI and 350 mg (1.00 mmol) of **44** in 8.5 mL of DMEU was heated in an oil bath at 100 °C (± 2 °C). After 36 h, GC analysis indicated that the reaction was complete. The crude reaction mixture was cooled, added to saturated NH_4Cl, and extracted with ether (3x). The combined organic layers were washed with NH_4Cl (2x), 5% Na_2SO_4 (1x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by PTLC, eluting with increasing concentrations of ether in hexanes to afford 233 mg (0.81 mmol, 82%) of the piperidinone product as a yellow oil. IR (thin film) 1732, 1651, 1595, 1493, 1382, 764, 697 cm^{-1}; ^1H NMR δ 7.37 (t, 2 H, *J* = 7.5 Hz), 7.24 (complex, 3 H), 4.17 (q, 2 H, *J* = 7.0 Hz), 3.72 (m, 1 H), 3.52 (ddd, 1 H, *J* = 13.9, 5.5, 1.8 Hz), 2.57 (dd, 1 H, *J* = 15.4, 2.8 Hz), 2.35 (tt, 1 H, *J* = 10.6, 2.8 Hz), 2.23 (dd, 1 H, *J* = 15.4, 10.6 Hz), 2.02 (dm, 1 H, *J* = 13.9 Hz), 1.93-1.81 (complex, 1 H), 1.35 (s, 3 H), 1.28 (t, 3 H, *J* = 7.0 Hz), 1.20 (s, 3 H); ^{13}C NMR δ 175.3, 172.7, 143.5, 128.9, 126.5, 126.1, 60.5, 49.9, 42.1,

39.5, 35.3, 25.5, 24.6, 21.7, 14.1; HRMS *m/e* for $C_{17}H_{23}NO_3$: calcd 289.1678. Found: 289.1673.

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.59; H, 7.96. Found: C, 70.69; H, 7.99.

Ethyl 3,4-Dihydro-3,3-dimethyl-2(1*H*)-quinolinone-4-acetate (55). The preparation of this compound was accomplished by heating 320 mg (1.00 mmol) of methyl (*E*)-2-(*N*-(2-(2-ethoxycarbonylethenyl)phenyl)carbamoyl)-2-methylpropanoate with 706 mg (4.00 mmol) of LiCl in 15 mL of DMEU for 23 h at 100 °C. The yield, after PTLC, was 199 mg (0.76 mmol, 76%) of the quinolinone as a light yellow solid, mp 110-112 °C. IR ($CHCl_3$) 3235, 1733, 1677, 1394, 1379, 758 cm^{-1}; ^1H NMR δ 8.93 (bs, 1 H), 7.16 (m, 2 H), 6.96 (t, 1 H, *J* = 7.6 Hz), 6.83 (d, 1 H, *J* = 7.7 Hz), 4.02 (m, 2 H), 3.14 (dd, 1 H, *J* = 10.2, 4.8 Hz), 2.71 (dd, 1 H, *J* = 14.8, 4.8 Hz), 2.32 (dd, 1 H, *J* = 14.8, 10.2 Hz), 1.30 (s, 3 H), 1.15 (s, 3 H), 1.13 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 176.1, 172.1, 135.7, 128.6, 127.8, 126.1, 123.0, 115.2, 60.5, 45.2, 40.6, 36.3, 25.2, 20.8, 14.0; HRMS *m/e* for $C_{15}H_{19}NO_3$: calcd 261.1402. Found: 261.1399.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.28. Found: C, 68.84; H, 7.24.

Ethyl 3,3-Dimethyl-1-phenyl-2-pyrrolidinone-4-acetate (56). The preparation of this compound was accomplished by heating 440 mg (1.32 mmol) of methyl (*E*)-2-(*N*-(3-ethoxycarbonyl-2-propenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate with 696 mg (5.28 mmol) of LiCl in 20 mL of DMEU for 12 h at 120 °C. The yield, after PTLC, was 109 mg (0.40 mmol, 30%) of the pyrrolidinone as a yellow oil. IR (thin film) 1736, 1707, 1597, 1494, 1392, 1377, 761, 696 cm^{-1}; ^1H NMR δ 7.64 (d, 2 H, *J* = 7.2 Hz), 7.35 (t, 2 H, *J* = 7.5 Hz), 7.13 (t, 1 H, *J* = 7.6 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.99 (dd, 1 H, *J* = 9.9, 7.3 Hz), 3.48 (dd, 1 H, *J*= 9.9, 8.8 Hz), 2.56 (m, 2 H), 2.38 (dd, 1 H, *J* = 16.5, 11.5 Hz), 1.29 (t, 3 H, *J* = 7.1 Hz), 1.25 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR δ 178.1, 172.0, 139.4, 128.7, 124.3, 119.6, 60.7, 50.5, 44.1, 39.3, 33.2, 23.7, 18.7, 14.1; HRMS *m/e* for $C_{16}H_{21}NO_3$: calcd 275.1558. Found: 275.1775.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.64. Found: C, 69.72; H, 7.62.

Chapter 6

Synthesis of ^{13}C-Labeled δ-Aminolevulinic Acids

Historical Background

Heme proteins represent a large class of biologically important molecules. The ability to study and characterize these proteins provides insight to disease and the most basic mechanisms of life itself.[103] The structure-function relationships of ferriheme proteins has been the focus of several studies using ^{1}H NMR spectroscopy.[104,105] The characterization of these heme proteins is difficult as the resonances required to elucidate the structure of the heme are buried under an aliphatic envelope of resonances that arise from other structures in the sample. It was recognized that observation of specific ^{13}C resonances from heme proteins could be very helpful in assigning the structure of the heme in it's bound *vs* unbound configuration.[106] However, due to the low natural abundance of ^{13}C, those resonances that would provide data are difficult to visualize. If the active sites being studied could be synthetically enriched with ^{13}C, then those required resonances would stand out significantly in the ^{13}C spectrum allowing for easier assignment.

The first committed precursor in the biosynthesis of heme proteins is δ-aminolevulinic acid (ALA).[107] A bacterial colony of *Escherichia coli* that has been transformed to express OM cytochrome b_5, could be supplied with isotopically enriched ALA, allowing for the biosynthesis of isotopically enriched OM cytochrome b_5.[103] This

particular strategy would require a source of reasonably pure, isotopically labeled ALA. Several labeled ALA derivatives are commercially available but prohibitively expensive. A study was therefore undertaken to synthesize a series of ^{13}C-labeled ALAs. A previously reported[108] synthesis of ^{13}C-labeled amino acids was modified to accommodate the needs of the current study. The position of the label within the amino acid was chosen so as to afford ^{13}C-enriched centers near the binding site of OM cytochrome b_5, allowing those resonances arising from labeled carbons to be assigned in the ^{13}C spectrum.

The general strategy developed for obtaining the amino acids was the same for all compounds synthesized. The syntheses differ only in 1) the reaction step where the label was inserted and 2) the labeled reagent used. For the 1-, 2-, and 1,2-labeled amino acids, the label was inserted during the final alkylation before hydrolysis. The label at C-3 was inserted using C-5-labeled Meldrum's acid[109] during the synthesis of ethyl γ-phthalimido-acetoacetate. The starting point for all of the syntheses was phthalimido acetic acid (**3**). Starting with phthalic anhydride (**1**) and glycine (**2**), acid **3** was produced after twenty minutes of reflux in mesitylene (Figure 1).

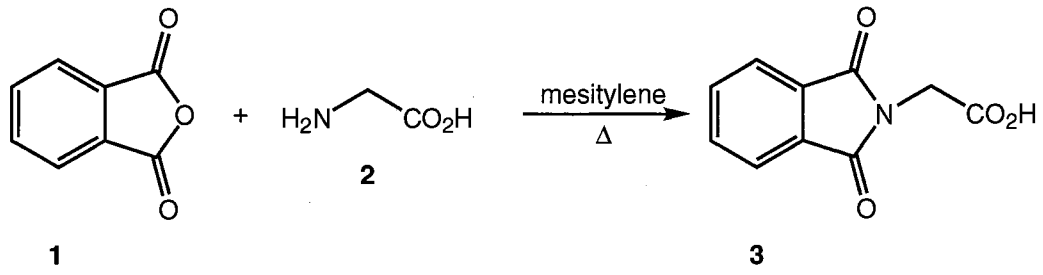


Figure 1. Synthesis of Phthalimidoacetic Acid.

In Figure 2, the β-keto ester **6** was accessed via reaction of the acid chloride **4** with Meldrum's acid **5**, followed by reflux in absolute EtOH which gave the ethyl γ-

phthalimido-acetoacetate (**6**). ALA's, labeled at C-3 would require the use of [5-^{13}C]-labeled Meldrum's acid in this reaction step to afford the [2-^{13}C] ethyl phthalimidoacetoacetate **7**. This labeled building block has been previously reported.[108]

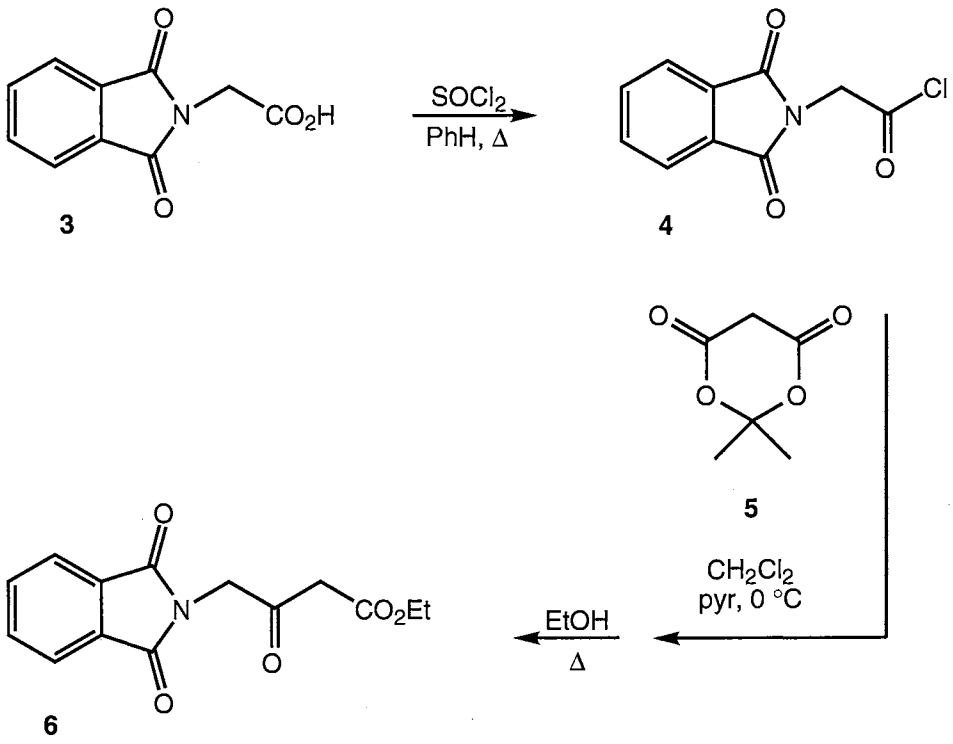


Figure 2. Synthesis of Ethyl Phthalimidoacetoacetate.

The labels at C-1 and C-2 were incorporated via an alkylation reaction. The 1- and 2-positions in the labeled aminolevulinic acids corresponded to the 1- and 2-positions of the ethyl bromoacetate derivatives. The 1-, 2-, and 1,2-labeled bromoesters were commercially available, with a certain amount of the 1-labeled ethyl bromoacetate being synthesized in our lab by esterification of a sample of C-1-labeled bromoacetic acid. Deprotonation of the activated methylene of **6** afforded the enolate which could be alkylated with the appropriate bromo ester to afford the phthalimido diester **8**. Figure 3 illustrates the general protocol for alkylation using a bromoester.

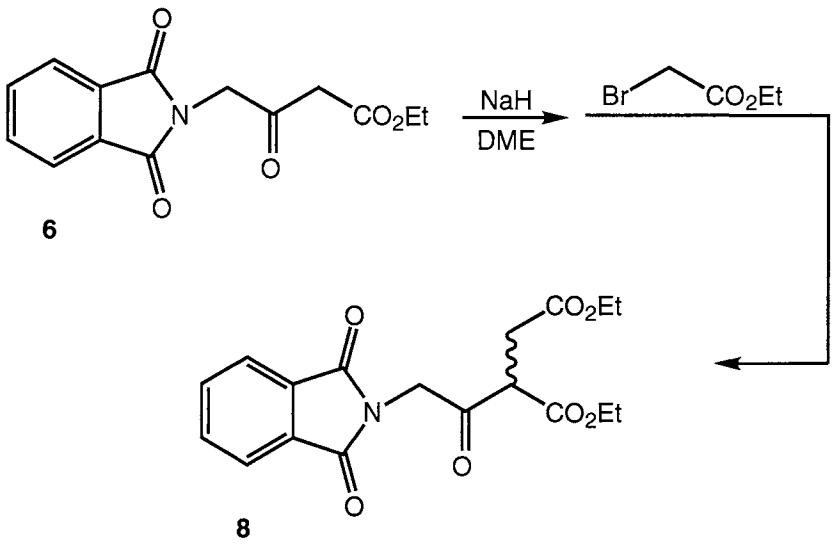
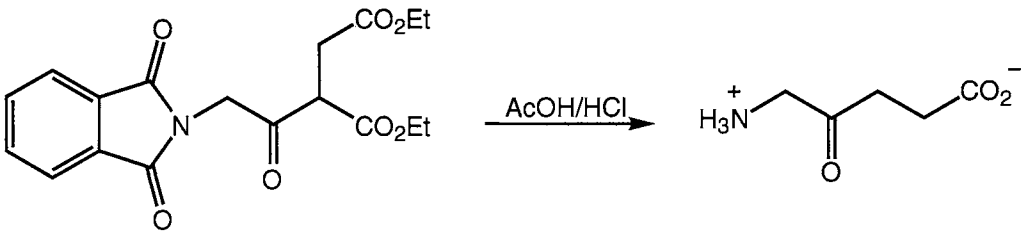


Figure 3. Alkylation of Ethyl Phthalimidoacetoacetate.

With the appropriately labeled phthalimido diester in hand, simple hydrolysis in 1:1 acetic acid:hydrochloric acid freed the labeled amino acid (Figure 4). A series of four labeled amino acids were synthesized. The labeled amino acids and their respective yields are summarized below in Table 1.



8	(non-labeled)	**13**	(non-labeled)
9	(C-1-labeled)	**14**	(C-1-labeled)
10	(C-1,2-labeled)	**15**	(C-1,2-labeled)
11	(C-2-labeled)	**16**	(C-2-labeled)
12	(C-2,3-labeled)	**17**	(C-2,3-labeled)

Figure 4. Hydrolysis/Decarboxylation of Phthalimido Diesters.

Labeled Diester	Labeled δ-ALA	Yield, %[a]
9 [1-^{13}C]	**14** [1-^{13}C]	63
10 [1,2-^{13}C]	**15** [1,2-^{13}C]	57
11 [2-^{13}C]	**16** [2-^{13}C]	40
12 [2,3-^{13}C]	**17** [2,3-^{13}C]	45

[a] Yields based on isolated purified product from one synthesis.

Table 1. Overall Yields of Labeled δ-Aminolevulinic Acids.

Experimental

Solvents were purified in the following manner: DME was stored under nitrogen over 4-Å molecular sieves, and distilled from $LiAlH_4$ immediately prior to use. THF was distilled from $LiAlH_4$. Other reagents were used as received. All reactions were run under dry N_2. Unless otherwise indicated, the saturated NaCl, and 0.5-1.0 *M* HCl used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) visualized using UV light, phosphomolybdic acid, or I_2 vapor or (2) capillary GC with FI detection (SE-30 column, 6-m x 0.25-mm i.d., 0.25-μm film thickness) programmed between 50-300 °C. Preparative separations were performed using one of the following methods: (1) flash chromatography[96] on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sylvania no. 2282), (2) ion-exchange chromatography using Dowex® 50X8-200 cationic exchange resin.[108] Band elution, where appropriate, was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra are referenced to polystyrene. ^{1}H NMR and ^{13}C NMR spectra were measured in either $CDCl_3$, D_2O, or DMSO-d_6 at 400 and 100 MHz, respectively, and, where appropriate, are referenced to internal $(CH_3)_4Si$. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Mass spectra of the final products were obtained under FAB conditions. Elemental analyses are ± 0.3%.

Phthalimidoacetic acid (3). A solution of 1.95 g (13.2 mmol) of phthalic anhydride and 0.99 g (13.2 mmol) of glycine in 25 mL of mesitylene was stirred for 20 min at 160 °C. The reaction mixture was cooled and the resulting white solid collected by vacuum filtration. Recrystallization from water gave 2.41 g (11.8 mmol, 89%) of **3** as a white solid, mp 193-194 °C. IR (thin film) 3266-2164, 1772, 1726, 737, 712 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.2 (bs, 1 H), 7.93 (m, 2 H), 7.89 (m, 2 H), 4.36 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 169.0, 167.4, 134.9, 131.5, 123.5, 38.9; HRMS *m/e* for $C_{10}H_7NO_4$: calcd 205.0375. Found: 205.0371.

Phthalimidoacetyl chloride (4). A solution of 1.91 g (9.3 mmol) of **3** and 5.54 g (3.4 mL, 46.6 mmol) of thionyl chloride in 20 mL of benzene was stirred at reflux for 12 h. The reaction was cooled and concentrated under vacuum. The resulting orange oil was redissolved in 25 mL of benzene and concentrated under vacuum (2x). The product was used without further purification, crude mp 77-78 °C; IR (thin film) 1804, 1771, 1727, 1608, 1403, 779, 718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (m, 2 H), 7.80 (m, 2 H), 4.83 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.1, 166.5, 134.6, 131.4, 123.9, 47.5; HRMS *m/e* for $C_{10}H_6{}^{35}ClNO_3$: calcd 223.0037. Found: 223.0032.

Meldrum's Acid (5). This compound was synthesized according to the procedure of Davidson and Bernhard.[109]

Ethyl γ-Phthalimidoacetoacetate (6). To a 0 °C solution of 1.40 g (9.7 mmol) of Meldrum's acid (**5**) in 2 mL of pyridine and 1 mL of CH_2Cl_2 was added 2.08 g (9.3 mmol) of **4** in 1 mL of CH_2Cl_2 dropwise over 1 h. The reaction was stirred as it warmed to rt. The reaction mixture was washed with 6 M HCl (1x), NaCl (1x), dried ($MgSO_4$) then concentrated under vacuum. The resulting orange solid was refluxed in 100 mL of absolute EtOH for 3 h. The reaction was concentrated under vacuum and the crude product was recrystallized from absolute EtOH to afford 2.01 g (7.31 mmol, 78%) of **6** as

light yellow needles, mp 110-111 °C. IR (thin film) 1774, 1745, 1722, 1416, 1392, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.75 (m, 2 H), 4.68 (s, 2 H), 4.23 (q, 2 H, *J* = 7.2 Hz), 3.60 (s, 2 H), 1.31 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 194.8, 167.4, 166.1, 134.2, 131.9, 123.5, 61.8, 46.8, 46.5, 13.9; HRMS *m/e* for $C_{14}H_{13}NO_5$: calcd 275.0793. Found: 275.0788.

[2-^{13}C] Ethyl γ-Phthalimidoacetoacetate (**7**). Same procedure as above using 1.10 g (7.64 mmol) of C-5-labeled Meldrum's acid, 4 mL of pyridine, 4 mL of CH_2Cl_2, and 1.63 g (7.3 mmol) of **4**. Recrystallization afforded 1.39 g (5.04 mmol, 68%) of **7** as yellow needles, mp 110-111 °C. IR (thin film) 1772, 1742, 1720, 1415, 1390, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (m, 2 H), 7.68 (m, 2 H), 4.60 (s, 2 H), 4.17 (q, 2 H, *J* = 7.1 Hz), 3.51 (d, 2 H, *J* = 131.1 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 4.69 (^{13}C-2); HRMS *m/e* for $^{12}C_{13}{}^{13}CH_{13}NO_5$: calcd 276.0827. Found: 276.0832.

Representative Procedure for Alkylation of Ethyl Phthalimidoaceto-acetate: Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate (**8**). To a stirred solution of 0.17 g (7.09 mmol) of NaH in 10 mL of DME was added 1.00 g (3.63 mmol) of **6** in 2 mL of DME dropwise at rt over 30 min. To this solution was added 0.73 g (4.37 mmol) of ethyl bromoacetate in 2 mL of DME dropwise over 30 min. The reaction was then allowed to stir for 12 h at 50 °C. The cooled reaction was poured into NH_4Cl and extracted with ether (3x). The combined organics were washed with NH_4Cl (2x), H_2O (1x), NaCl (1x), dried ($MgSO_4$) and concentrated under vacuum. The crude product was flash chromatographed on a silica gel column eluted using increasing concentrations of ether in hexanes to give 0.70 g (1.94 mmol, 53%) of white solid, mp 72-74 °C. IR (thin film) 1772, 1742, 1719, 1410, 1389, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.74 (m, 2 H), 4.94 (d, 1 H, *J* = 18.0 Hz), 4.73 (d, 1 H, *J*= 18.0 Hz), 4.28 (m, 2 H), 4.17 (m, 3 H), 3.02 (dd, 1 H, *J* = 17.7, 7.9 Hz), 2.95 (dd, 1 H, *J* = 17.7, 6.5 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 196.7, 170.8, 167.4, 167.2, 134.2,

132.0, 123.5, 62.4, 61.2, 51.6, 46.7, 32.1, 14.0, 13.9; HRMS *m/e*for $C_{18}H_{19}NO_7$: calcd 361.1161. Found: 361.1149.

[1-^{13}C] Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate (9): 1.48 g (4.09 mmol, 69%). The spectral data matched those reported by Kurumaya.[108]

[1,2-^{13}C] Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate (10): 1.42 g (3.91 mmol, 66%), mp 71-72 °C; IR (thin film) 1772, 1741, 1718, 1412, 1387, 716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.74 (m, 2 H), 4.94 (d, 1 H, *J* = 18.0 Hz), 4.28 (m, 2 H), 4.17 (m, 3 H), 2.99 (dm, 2 H, *J* = 132.4 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.8 (d, ^{13}C-1, *J* = 58.9 Hz), 32.1 (d, ^{13}C-2, *J* = 58.9 Hz); HRMS *m/e* for $^{12}C_{16}{}^{13}C_2H_{19}NO_7$: calcd 363.1228. Found: 363.1224.

[2-^{13}C] Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate (11): 0.98 g (2.7 mmol, 46%). The spectral data matched those reported by Kurumaya.[108]

[2,3-^{13}C] Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate (12): 1.27 g (3.50 mmol, 69%), mp 70-72 °C; IR (thin film) 1770, 1740, 1717, 1412, 1388, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.74 (m, 2 H), 4.94 (d, 1 H, *J* = 18.0 Hz), 4.73 (d, 1 H, *J* = 18.0 Hz), 4.28 (m, 2 H), 4.16 (q, 2 H, *J* = 7.2 Hz), 4.17 (dm, 1 H, *J* = 123.3 Hz), 2.99 (dm, 2 H, *J* = 132.2 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 51.6 (d, ^{13}C-3, *J* = 38.7 Hz), 32.1 (d, ^{13}C-2, *J* = 39.0 Hz). HRMS *m/e* for $^{12}C_{16}{}^{13}C_2H_{19}NO_7$: calcd 363.1228. Found: 363.1221.

Representative Procedure for Hydrolysis-Decarboxylation of Ethyl 3-Ethoxycarbonyl-4-oxo-5-phthalimidopentanoate: δ-Aminolevulinic Acid Hydrochloride (13): A solution of 0.67 g (1.86 mmol) of **8** in 9 mL of 1:1 AcOH:HCl was stirred at reflux for 24 h. The cooled reaction mixture was concentrated under vacuum. The resulting tan solid was dissolved in 30 mL of distilled water and reconcentrated. The off-white solid was dissolved in 25 mL of distilled water and washed with EtOAc (3x). The aqueous layer was concentrated under vacuum. The crude amino acid was chromatographed using Dowex® 50X8-200 cationic-exchange resin. A typical procedure

involved rinsing 20 mL (solid volume) of the resin with 0.001 M HCl to remove unwanted solids and to activate the resin. The resin was packed onto a medium glass-fritted column using 0.001 M HCl as the solvent. The crude amino acid was dissolved in 1 mL of 0.001 M HCl and loaded on top of the resin plug. The crude amino acid was eluted with 0.001 M HCl which, at pH = 3, is above the pKa of the carboxylate of the amino acid and causes the desired product to adhere to the column packing. After ten volumes (equivalent to column packing volume, 200 mL) of 0.001 M HCl, the eluting solvent was changed to 1 M HCl. At pH = 0 (below the pKa of the desired acid) the pure amino acid is released from the column and collected as fractions that can be spotted and visualized using a ninhydrin solution as the developer. Using this purification method, 244 mg (1.86 mmol, 96%) of non-labeled δ-ALA was obtained, mp 151-152 °C (dec); IR (thin film) 3610-2141, 1718 cm^{-1}; ^{1}H NMR (D_2O) δ 4.12 (s, 2 H), 2.90 (t, 2 H, J = 6.3 Hz), 2.72 (t, 2 H, J = 6.3 Hz); ^{13}C NMR (D_2O) δ 206.8, 179.4, 49.7, 36.9, 29.9; MS-FAB *m/e* 132 (M^++1).

[1-^{13}C]-δ-Aminolevulinic Acid Hydrochloride (14): 524 mg (3.97 mmol 97%). The spectral data matched those reported by Kurumaya.[108]

[1,2-^{13}C]-δ-Aminolevulinic Acid Hydrochloride (15): 341 mg (2.57 mmol 91%), mp 150 °C (dec); IR (thin film) 3600-2133, 1717 cm^{-1}; ^{1}H NMR (D_2O) δ 3.93 (s, 2 H), 2.68 (s, 2 H), 2.53 (dq, 2 H, J = 141.4, 6.5 Hz); ^{13}C NMR (D_2O) δ 177.8 (d, ^{13}C-1, J = 54.5 Hz), 28.3 (d, ^{13}C-2, J = 55.2 Hz); MS-FAB *m/e* 134 (M^++1).

[2-^{13}C]-δ-Aminolevulinic Acid Hydrochloride (16): 324 mg (2.46 mmol 91%). The spectral data matched those reported by Kurumaya.[108]

[2,3-^{13}C]-δ-Aminolevulinic Acid Hydrochloride (17): 433 mg (3.25 mmol 95%), mp 151 °C (dec); IR (thin film) 3605-2108, 1718 cm^{-1}; ^{1}H NMR (D_2O) δ 4.21 (s, 2 H), 2.68 (dq, 2 H, J = 140.4, 6.3 Hz), 2.53 (dq, 2 H, J = 132.7, 6.8 Hz); ^{13}C NMR (D_2O) δ 52.6 (d, ^{13}C-3, J = 54.5 Hz), 28.3 (d, ^{13}C-2, J = 55.2 Hz); MS-FAB *m/e* 134 (M^++1).

Conclusion

A series of four ^{13}C-labeled δ-aminolevulinic acids were synthesized using a modified procedure. It should be noted that the compounds were obtained at a considerably lower cost than the commercially available δ-ALAs. These compounds were successfully incorporated into heme proteins and subsequently characterized via ^{13}C NMR.

REFERENCES

1. Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, **1991**.

2. Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, **1968**; p. 42.

3. Paquette, L. A.; Wang, H.-L. *J. Org. Chem.*, **1996**, *61*, 5352-5357.

4. Cho, B. P.; Zhou, L. *Tetrahedron Lett.*, **1996**, *37*, 1535-1538.

5. Krow, G. R. *Tetrahedron* **1987**, *43*, 3-38.

6. Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.*, **1979**, *101*, 4003-4005.

7. Stevenson, R. B.; Chiu, Y. *Heterocycles* , **1996**, *43*, 619-624.

8. Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, **1968**; p. 101.

9. Geier, M.; Hesse, M. *Synthesis* , **1990**, 56-58.

10. Koldobskii, G.; Tereschchenko, G. F.; Gerasimova, E. S.; Bagal, L. I. *Zh. Org. Khim.*, **1970**, *6*, 2395-2401.

11. Krow, G. R. *J. Org. Chem.*, **1996**, *61*, 5574-5580.

12. Bhawal, B. M.; Mayabhate, S. P.; Likhite, A. P.;Deshmukh, A. R. A. S. *Synth. Commun.*, **1995**, *25*, 3315-3321.

13. Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.*, **1979**, *101*, 6289-6291.

14) a) Pavel, P. *Czech, Patent CS* 258,178, **1989** (*Chem. Abstr.* **1989**, *111*, 232786z). b) Rafila, D.; Rozalia, K. *Rom. Patent RO* 96,343, **1990** (*Chem. Abstr.* **1990**, *112*, 55845r).

15. Demnitz, F. W. J.; Philippini, C.; Raphael, R. A. *J. Org. Chem.*, **1995**, *60*, 5114-5120.

16. Fischer, R. H.; Weitz, H. M. *Synthesis*, **1980**, 261-282.

17. Nakashita, Y.; Hesse, M. *Helv. Chim. Acta.*, **1983**, *66*, 845-860.

18. Posner, G. H.; Asirvatham, E. *Tetrahedron Lett.*, **1986**, *27*, 663-666.

19. Posner, G. H. *Chem. Rev.*, **1986**, *86*, 831-844.

20. Blechert, S. *Nachr. Chem. Tech. Lab.*, **1980**, *28*, 110-111.

21. Back, T. G. *Tetrahedron* , **1977**, *33*, 3041-3059.

22. Nicolaou, K. C. *Tetrahedron* , **1977**, *33*, 683-710.

23. Masamune, S.; Bates, G. S.; Corcoran, J.W. *Angew. Chem. Int. Ed. Engl.*, **1977**, *16*, 585-607.

24. Paterson, I.; Mansuri, M. M. *Tetrahedron* , **1985**, *41*, 3569-3624.

25. Stach, H.; Hesse, M. *Helv. Chim. Acta.*, **1987**, *70*, 315-320.

26. Wälchi, R.; Guggisberg, A.; Hesse, M. *Tetrahedron Lett.*, **1984**, *25*, 2205-2208.

27. Lewin, G.; Schaeffer, C.; Lambert, P. H. *J. Org. Chem.*, **1995**, *60*, 3282-3287.

28. Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.*, **1992**, *33*, 5705-5708.

29. Bunce, R. A. *Tetrahedron*, **1995**, *51*, 13103-13159.

30. Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 131-312

31. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.*, **1996**, *96*, 195-206.

32. Ziegler, F. *Chem. Rev.*, **1988**, *88*, 1423-1452.

33. Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc., Chem. Comm.*, **1985**, 1047-1051.

34. Ong, C. W.; Chen, C. M.; Juang, S. S. *J. Org. Chem.*, **1994**, *59*, 7915-7916.

35. Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.*, **1992**, *57*, 5049-5051.

36. Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.*, **1989**, *30*, 4829-4832.

37. Ulrich, H.; Rao, D. V. *J. Org. Chem.*, **1977**, *42*, 3444-3445.

38. Hagiwara, H.; Akama, T.; Okano, A.; Uda, H. *Chem. Lett.*, **1988**, 1793-1796.

39. Cory, R. M.; Renneboog, R. M. *J. Org. Chem.*, **1984**, *49*, 3898-3904.

40. Robinson, R.; Cornforth, J. W. *J. Chem. Soc.*, **1949**, 1955-1959.

41. Stork, G.; Loewenthal, H. J. E.; Mukharji, P. C. *J. Am. Chem. Soc.*, **1956**, *78*, 501-502.

42. Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.*, **1972**, *94*, 5109-5110.

43. Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.*, **1987**, *28*, 6671-6674.

44. Ho, T.-L. *Tandem Organic Reactions*, Wiley: New York; **1992;** p. 416.

45. Kuehne, M. E.; Reider, P. J. *J. Org. Chem.*, **1985**, *50*, 1464-1467.

46. Negishi, E.; Coperét, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.*, **1996**, *96*, 365-393.

47. Balme, G.; Bouyssi, D. *Tetrahedron*, **1994**, *50*, 403-414.

48. Molander, G. A.; Harris, C. R. *Chem. Rev.*, **1996**, *96*, 307-338.

49. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.*, **1987**, 1485-1490.

50. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.*, **1980**, *102*, 2693-2698.

51. Molander, G. A.; McKie, J. A. *J. Org. Chem.*, **1993**, *58*, 7216-7227.

52. Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.*, **1995**, *117*, 3705-3716.

53. Tietze, L. F. *Chem. Rev.*, **1996**, *96*, 115-136.

54. Bunce, R. A.; Wamsley, E. J.; Pierce, J. P.; Shellhammer, A. J.; Drumright, R. E. *J. Org. Chem.*, **1987**, *52*, 464-466.

55. Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.*, **1992**, *57*, 1727-1733.

56. Bunce, R. A.; Bennet, M. J. *Synthetic Commun.*, **1993**, *23*, 1009-1110.

57. Bunce, R. A.; Harris, C. R. *J. Org. Chem.*, **1992**, *57*, 6981-6985.

58. Bunce, R. A.; Chase, C. *unpublished results.*

59. Eilerman, R. G.; Willis, B. J. *J. Chem. Soc., Chem. Commun.*, **1981**, 30-32.

60. Bunce, R. A.; Dowdy, E. D.; Jones, P. B.; Holt, E. M. *J. Org. Chem.*, **1993**, *58*, 7143-7148.

61. Takei, S.; Kawano, Y. *Tetrahedron Lett.*, **1975**, *49*, 4389-4392.

62. a) March, J. *Advanced Organic Chemistry*, 4th el., Wiley: New York, **1992**; p. 275. b) Isaacs, N. S. *Physical Organic Chemistry*, Wiley: New York, **1987**; p. 287.

63. Based upon studies of cyclohexane derivatives, Me is sterically larger than CN, CO_2Et and COMe, approximately isosteric with COPh, and sterically smaller than SO_2Ph; see: a) Hirsch, J. A. *Top. Stereochem.*, **1967**, *1*, 199-222. b) Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.*, **1971**, *3*, 139-194.

64. Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.*, **1986**, *51*, 2671-2675.

65. Bunce, R. A.; Harris, C. R. *Synthetic Commun.*, **1996**, *26*, 1969-1975.

66. a) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.*, **1975**, *40*, 2165-2170. b) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Lai, C.-S. *J. Org. Chem.*, **1992**, *57*, 2018-2029.

67. Bunce, R. A.; Dowdy, E. D.; Jones, P. B.; Childress, R. S. *unpublished results.*

68. March, J. *Advanced Organic Chemistry*, 4th ed., Wiley: New York, **1992**; p. 21.

69. Ellis, G. P. *Chromans and Tocopherols*; Wiley: New York, **1981**; Vol. 36.

70. Aukrust, I.; Skättebol, L. *Acta. Chem. Scand.*, **1996**, *50*, 132-140.

71. Deshpande, P. P.; Baker, D. C. *Synthesis*, **1995**, 630-632.

72. Talley, J. J. *J. Org. Chem.*, **1985**, *50*, 1695-1699.

73. Childress, R. S. Ph.D Thesis Dissertation **1996**.

74. Bunce, R. A.; Schilling, C. L. III *J. Org. Chem.*, **1995**, *60*, 2748-2752.

75. Bunce, R. A.; Peeples, C. J.; Holt, E. M. *unpublished results.*

76. Chakraborty, D. P.; Das, K. C. *Tetrahedron Lett.*, **1968**, *48*, 5015-5018.

77. a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.*, **1978**, 499-502. b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.*, **1978**, *31*, 38-42. c) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *J. Antibiot.*, **1982**, *35*, 783-787.

78. Vandewalle, M.; Dewanckele, J. M.; Zutterman, R. *Tetrahedron*, **1983**, *39*, 3235-3244.

79. Little, R. D.; Sowell, C. G.; Wolin, R. L. *Tetrahedron Lett.*, **1990**, *31*, 485-488.

80. Pinto, A. C.; Epifanio, R. de A.; Camargo, W. *Tetrahedron Lett.*, **1988**, *29*, 6403-6406.

81. Umarani, D. C.; Seshadri, R.; Gore, G.; Chakravarti, K. K.; *Flavour Ind.* **1970**, *1*, 623-625.

82. Mori, K.; Sakurai, K.; Kitahara, T. *Tetrahedron*, **1988**, *44*, 6581-6588.

83. Liu, H.-J.; Chan. W. W. *Can. J. Chem.*, **1979**, *57*, 708-709.

84. Chan, W. W.; Liu, H.-J. *Can. J. Chem.*, **1982**, *60*, 1081-1091.

85. Teisseire, P.; Maupetit, P.; Corbier, B. *Recherches*, **1974**, *19*, 8-12.

86. Liu, H.-J.; Ralitsch, M. *J. Chem. Soc., Chem. Commun.*, **1990**, 997-999.

87. Connolly, J. D.; Overton, K. H.; Polonsky, W. *J. Progr. Phytochem.*, **1970**, *2*, 385.

88. Ekong, D. E. U.; Obasi, M. E.; Okogun, J. I. *J. Chem. Soc., Perkin Trans. 1*, **1972**, *15*, 1943-1946.

89. Spreitzer, H. *Monatsh. Chem.*, **1990**, *121*, 847-851.

90. Ireland, R. E.; Grand, P. S.; Dickerson, R. E.; Bordner, J.; Rydjeski, D. R. *J. Org. Chem.*, **1970**, *35*, 570-584.

91. Engel, P. S.; Schexnayder, M. A. *J. Am. Chem. Soc.*, **1975**, *97*, 145-153.

92. a) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.*, **1955**, *77*, 1028-1032. b) Rinehart, K. L. Jr.; Perkins, E. G.; *Organic Syntheses*; Wiley: New York, **1963**; Collect. Vol. IV, p. 444-450. c) Bunce, R. A.; Childress, R. S. *Org. Prep. Proc. Int.*, **1995**, *27*, 122-125.

93. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.*, **1974**, *96*, 1082-1087.

94. Inomata, K.; Aoyama, S.; Kotake, H. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 930-932.

95. For non-UV active compounds, PTLC plates were visulized with I_2 vapor and the separated bands were cut from the plates and extracted with ether. The ether extract was washed with 5% $Na_2S_2O_3$ and NaCl, dried ($MgSO_4$), and concentrated.

96. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923-2925.

97. Leopold, E. J. *J. Org. Chem.*, **1982**, *47*, 4592-4594.

98. Prepared from dimethyl malonate by the method of Strube, R. E. *Organic Syntheses*; Wiley: New York, **1963**; Collect. Vol. IV, pp. 417-419.

99. Bunce, R. A.; Moore, J. D. *Org. Prep. Prac. Int. submitted.*

100. a) Kjær, A.; Jensen, R. B. *Acta Chem. Scand.*, **1956**, *10*, 1365-1371. b) Kharasch, M. S.; Fuchs, C. F. *J. Org. Chem.*, **1944**, *9*, 359-372.

101. Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.*, **1992**, *57*, 7056-7066.

102. Foy, B. D.; Smudde, R. A.; Wood, W. F. *J. Chem. Ed.*, **1993**, *70*, 322.

103. Rivera, M.; Walker, F. A. *Anal. Biochem.*, **1995**, *230*, 295-302.

104. de Ropp, J. S., Yu, L. P.; La Mar, G. N. *J. Biomol. NMR*, **1991**, *1*,1545-1556.

105. Emerson, S. D.; La Mar, G. N. *Biochemistry*, **1990**, *29*, 1556-1566.

106. La Mar, G. N.; de Ropp, J. S. *Biological Magnetic Resonance*; Plenum:New York, **1993**.

107. Rivera, M., Barillas-Mury, C., Christensen, K. A., Little, J. W.; Wells, M. A., Walker, F.A. *Biochemistry*, **1992**, *31*, 12233-12239.

108. Kurumaya, K.; Okazaki, T.; Seido, N.; Akasaka, Y.; Kawajiri, Y.; Kajiwara, M. *J. Labelled Compd. and Radiopharm.*, **1989**, *27*, 217-235.

109. Davidson, D.; Bernhard, S. A.; *J. Am. Chem. Soc.*, **1948**, *70*, 3426-3428.

VITA

Curtis L. Schilling III

Candidate for the Degree of

Doctor of Philosophy

Thesis: I. A TANDEM DEALKOXYCARBONYLATION-MICHAEL ADDITION ROUTE TO HIGHLY FUNCTIONALIZED CYCLOHEXANEACETIC ESTERS. II. A TANDEM DEALKOXYCARBONYLATION-MICHAEL ADDITION ROUTE TO LACTAMS AND LACTONES. III. THE SYNTHESIS OF ^{13}C-LABELED δ-AMINOLEVULINIC ACIDS.

Major Field: Chemistry

Biographical

Personal Data: Birthdate; August 6, 1963 in Syracuse, New York, the son of Curtis L. Jr. and Betty Anne Schilling; Married to Tracy Ann Schilling

Education: Graduated from Croton-Harmon High School, Croton-on-Hudson, New York in June 1981; received Bachelor of Science in Chemistry from the State University of New York, College at Oswego, in December 1989.

Awards: Dean's List (1987); Conoco Fellowship (Summer 1993); Skinner Fellowship (1994-96); Jonas Distinguished Graduate Fellowship (1996)

Societies & Committees: American Chemical Society Student Affiliate (1987-89); American Chemical Society Member (1992-present); Phi Lambda Upsilon (member 1992-present, President 1994); Graduate Student Association Representative (1994); Phi Kappa Phi (1996); Sigma Xi (1996)

Professional Experience: Manager, Organic Stockroom, Oklahoma State University (Spring 1996); Teaching/Research Assistant, Oklahoma State University (1992-1996); Technician, Union Carbide Corporation, Tarrytown, NY Synthetic Division of the Plastics Additives Systems Group (1989-1992)