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THE DEVELOPMENT OF TANDEM DECARBOXYLATION MICHAEL ADDITIONS IN ORGANIC SYNTHESIS

BY

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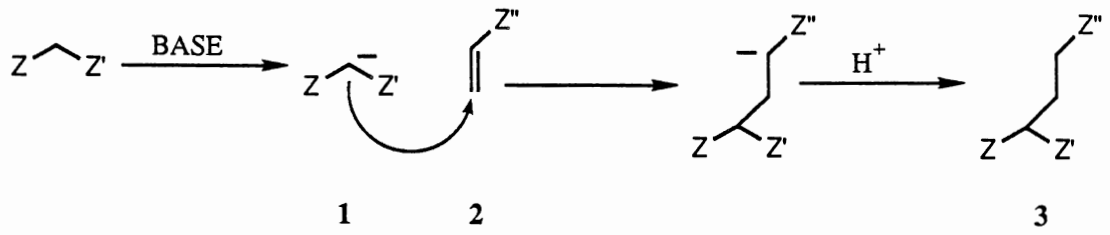
CHAPTER I

HISTORICAL

The development of new synthetic methodologies is one of the most important areas of research in synthetic organic chemistry. This can involve the optimization of known reactions through the alteration of reaction conditions, or the development of new reactions, to produce a desired target molecule. One of the best ways to improve the efficiency of a reaction scheme is to produce more than one carbon-carbon bond in one or more of the synthetic steps. There are many known transformations that meet this criteria; cycloadditions, annulations, and dialkylations.[1] When two different types of reactions are carried out in a single pot, this process is termed a tandem reaction. The focus of this investigation is tandem processes that are either initiating or terminating in a Michael Addition.

MICHAEL REACTIONS

The Michael reaction is one of the most common reaction processes used in the formation of carbon-carbon bonds.[2] Michael reactions involve the conjugate addition of a nucleophile to an unsaturated system that is conjugated with an electron withdrawing group such as nitriles, esters, ketones, aldehydes, and sulfones.[3] These reactions are not without their limitations; there can be multiple enolates formed, polymerizations, and competing side reactions such as 1,2-additions and condensation reactions. In the classic Michael reaction, a molecule containing an electron withdrawing group is initially treated with a base to generate an anion **1** (See Figure 1). An olefin, also containing an electron

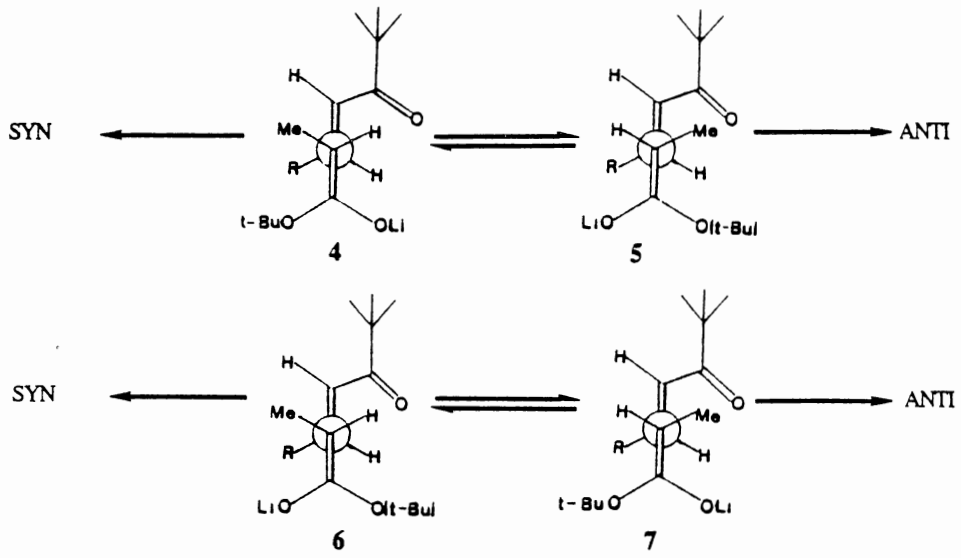


1 2 3

Figure 1. Mechanism of the Michael Addition

withdrawing group **2**, is added and a 1,4-conjugate addition occurs. The reaction mixture is then treated with a proton source to yield the neutral product **3**.

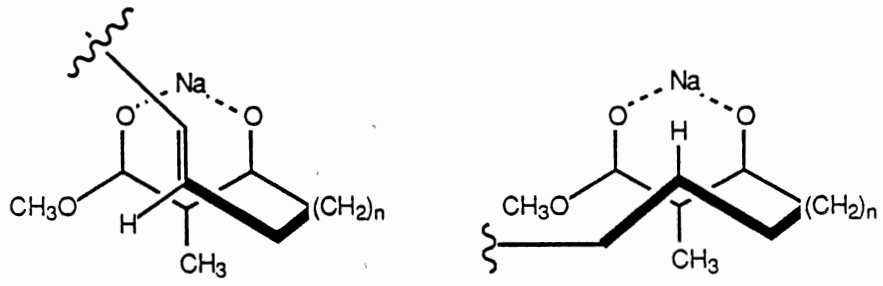
Michael processes have been used in the synthesis of numerous natural and un-natural products. One advantage of using this reaction is the development of conditions that give the correct regio- and stereocontrol. This is usually accomplished through the generation of either the kinetic or the thermodynamic enolate, or through specific control of the stereochemistry of the Michael acceptor. Heathcock and co-workers studied the stereo-chemistry of Michael additions involving lithium enolates.[4] The geometry of the enolate and the conjugate addition adducts were examined by reacting a substituted acrylic ester with either the kinetic or the thermodynamic enolate of *tert*-butyl propionate. The kinetic enolate was generated in THF -78°C, while the thermodynamic enolate was generated in THF containing 23% hexamethylphosphoric triamide (HMPT). The diastereomeric ratios of the products were determined by capillary GC. Through the analysis of these products four open transition states were proposed (See Figure 2). The adducts arising from the kinetic *E* enolate, **4** and **6**, were generally syn, while the Z enolate, transition states **5** and **7**, gave predominately the anti isomer. The steric interactions between either the t-BuO or the LiO, and the R group on the molecule were thought to control the stereochemistry of the products. It was proposed that the enolate exists in solution as a cubic tetramer which would explain the bias of transition states and the stereocontrol of the reaction.



4 5 6 7

Figure 2. Transition States of the Michael Addition

Michael additions can also be intramolecular processes. For the intramolecular process to occur, a molecule must be designed with both a Michael donor, an enolate, and a Michael acceptor in the same system. Stork and co-workers have elegantly showed the use of this intramolecular process to form 2,3-disubstituted cyclopentanones and cyclohexanones.[5] In his study, a series of β-ketoesters, with an internal double bond three or four carbons away, were cyclized using either potassium *tert*-butoxide in *tert*-butyl alcohol



8 9

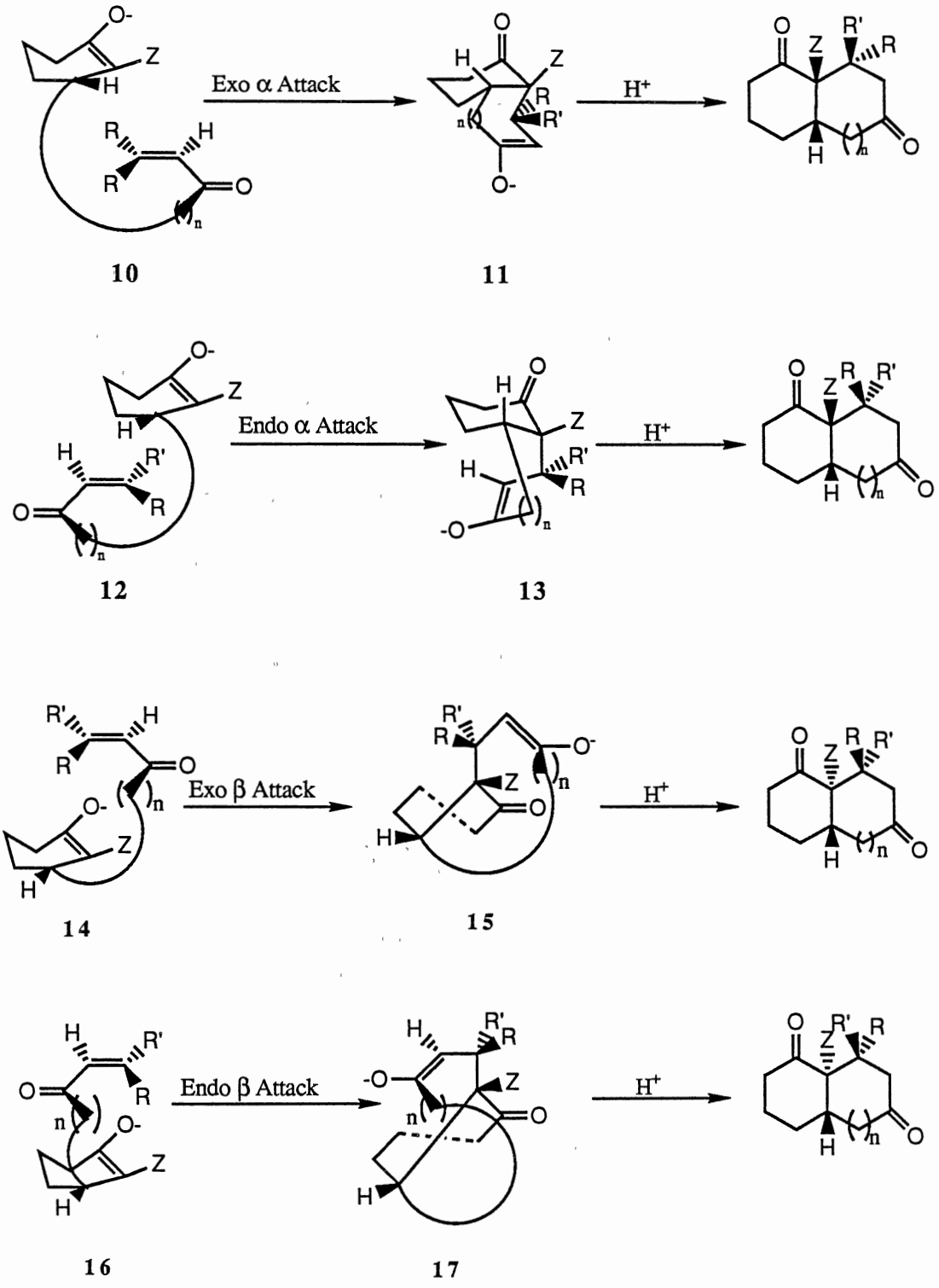
Figure 3. Transition States for Intramolecular Michael Additions

to give a 1:1 ratio of the cis and trans isomers, or with sodium methoxide in methanol to give a 3:1 ratio in favor of the cis isomer. The use of a catalytic amount of sodium hydride in benzene, however, gave a 90% yield of only the trans isomer of the cyclopentanone, and

a 30:1 ratio in favor of the cis isomer for the cyclohexanone. The stereospecificity of this reaction is due to the formation of a metal chelate that leads to a favored cyclic transition state (See Figure 3). The high amount of stereocontrol can be explained by the stabilized transition state **9** where the acceptor chain is pointed away from the six-membered chelate and the steric interactions are reduced.[5]

Another type of cyclization was termed a "Michael Initiated Ring Closure", or MIRC, in 1980 by Little.[6] In his investigation, sulfur and nitrogen nucleophiles were used to initiate a reaction with ω-halo-2-alkenoates to form β-heteroatom-substituted cycloalkyl esters of three-, five- six-, and seven-membered rings. The use of lithium alkylthiolates led to three-membered rings, while attempts to form six- and seven-membered rings resulted in double additions and S_N2 reactions. The use of LDA as a base afforded the five-, six-, and seven-membered rings, with decreased yields for the seven-membered rings most likely due to entropic effects. Attempts to form four-membered rings were unsuccessful due to competing side reactions such as eliminations and polymerizations.[6]

The transition states of Michael processes become very complex when the enolate is part of a cyclic system. There are many conformational and steric effects that can control the stereochemistry of the adduct. The intramolecular attack of a cyclic enolate on an enone can take place through four cyclic transition states (See Figure 4) that are analogous to the transition states of the non-cyclic system. For five- and six-membered rings, the endo additions are predominant resulting in the cis fusion. The preference for the cis isomer can be explained by the boat-like conformations **11** and **13** that relieve any flag-pole or diaxial interactions. When the starting material is a five-membered ring, formation of a new, fused seven-membered ring results in a cis junction, presumably through a transition state similar to **11** or **13**. When a seven-membered ring is fused to a six-membered ring, the cis isomer is the major product with a small but isolable amount of the trans isomer formed.[7] The torsional mobility of the seven-membered ring allows for relief of any steric hindrance in the transition states **15** and **17**.[7]

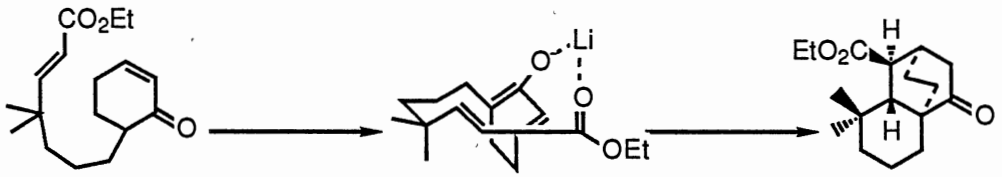


n=1-3 Z= Electron withdrawing group R=alkyl group

Figure 4. Transition States for Cyclic Intramolecular Michael Additions

TANDEM REACTIONS

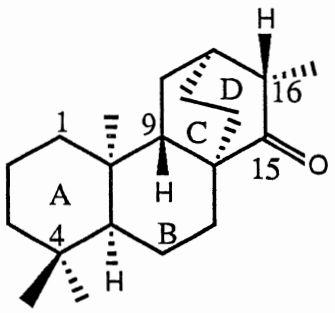
The use of Michael processes in conjunction with a second reaction are called tandem reactions and are well documented. They have been used in the synthesis of many different types of natural products. Kametani and co-workers[8-10] used an intramolecular double Michael reaction to form the spiro-fused bicyclo[2.2.2]octane **20** which is a useful intermediate for the synthesis of many complicated natural products. This reaction, illustrated in Figure 5, uses the lithium enolate of a 6-substituted 2-cyclohexenone, **18**. A lithium chelate in the intermediate **19** controls the stereochemistry of the product,



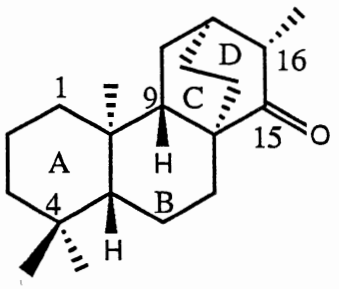
18 **19** **20**

Figure 5. Transition State for Bicyclo[2.2.2]octane Formation

which is consistent with sequential Michael additions. Kametani was able to use this sequence in the synthesis of an isoatisirene, which contains a perhydroethanophenanthrene skeleton with the 2-carbon bridge on the C ring which is trans to the hydrogen at the BC ring juncture[9] (See Figure 6). Antisiran-15-one was also synthesized using tandem Michael additions.[10] By carefully selecting the starting materials and the reactants all of the chiral centers are set during the reaction sequence. Two of the chiral centers are locked by using *trans*-7,7-dimethylbicyclo[4.4.0]decan-10-one as the starting material. Using a nine step reaction sequence, antisiran-15-one was isolated as a single optical isomer. Isolating this compound as a single isomer was quite significant considering that there are six chiral centers in the molecule, three of which were selectively generated during the tandem Michael additions.



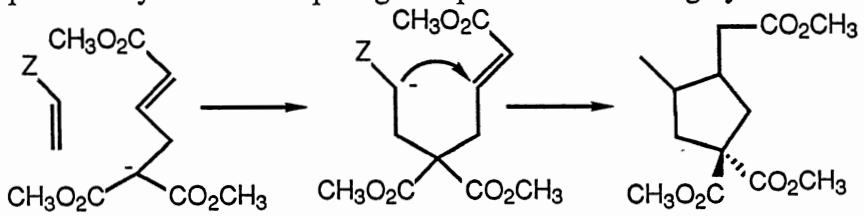
Isoatisirene



Atisiran-15-one

Figure 6. Structures of Isoatisiran and Atisiran-15-one

The formation of five-membered rings is a frequent goal in organic synthesis. These systems have been synthesized using two sequential Michael reactions.[12] The key to this synthesis was the design of the precursor molecule, the Michael donor and acceptor were placed less than three carbons apart. Ring strain prevented these two moietes from prematurely cyclizing to a three-membered ring by an intramolecular Michael addition. Bunce and co-workers[12] used these reactions on both cyclic and alicyclic systems (See Figure 7). The substituted malonate anion **21** was reacted with methyl and phenyl vinyl ketones. The initial adduct **22** having an anion α to the carbonyl, cyclized intramolecularly with the acrylate double bond on the malonate substituent to form the highly substituted cyclopentane **23**. The alicyclic systems generally gave higher yields than the cyclic systems. The limiting factors were presumed to be the steric environment at the β position of the acceptor moiety and the competing retroprocesses in the highly hindered substrates.[12]



21 **22** **23**

Figure 7. The Formation of Cyclopentanes by Tandem Michael Reactions

This reaction also gave a high degree of stereoselectivity. The stereochemistry of the ring juncture, when the cyclic systems were used, was cis in the five-five system, while the six-five system gave a 9:1 ratio of products in favor of the trans isomer.

Tandem reactions using an initial Michael reaction, followed by a different type of process have also been useful in the synthesis of many different molecules. For example,

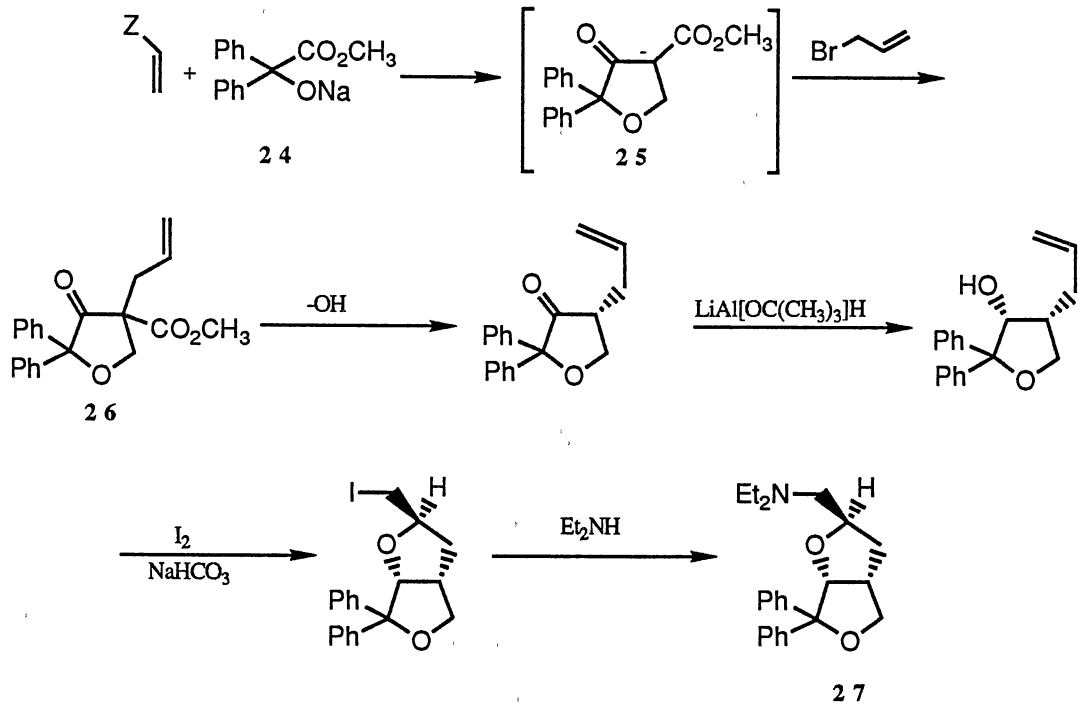


Figure 8. Synthesis of 2-[(Diethylamino)methyl]-6,6-diphenylhexahydro[3,4-b]furan

Flavin and Lu have used a Michael addition, followed by a Dieckmann cyclization, to form 2-[(diethylamino)methyl]-6,6-diphenylhexahydrofuro[3,4-b]furan (**27**). This molecule is of interest as a precursor to muscarinic cholinergic receptor probes.[13] The synthesis, found in Figure 8, involves the Michael addition of methyl acrylate to methyl sodium benzilate, **24** in DMSO. The resulting anion cyclizes via a Dieckmann condensation to form the β-ketoester **25**. This was then reacted with allyl bromide to give **26**. After decarboxylation, reduction to the alcohol, iodine-promoted cyclization, and nucleophilic substitution with diethylamine, the target molecule **27** was formed.

Posner has developed the use of multiple tandem Michael reactions for the synthesis of many natural products.[14-17] In his series of papers, Posner has shown that as many as

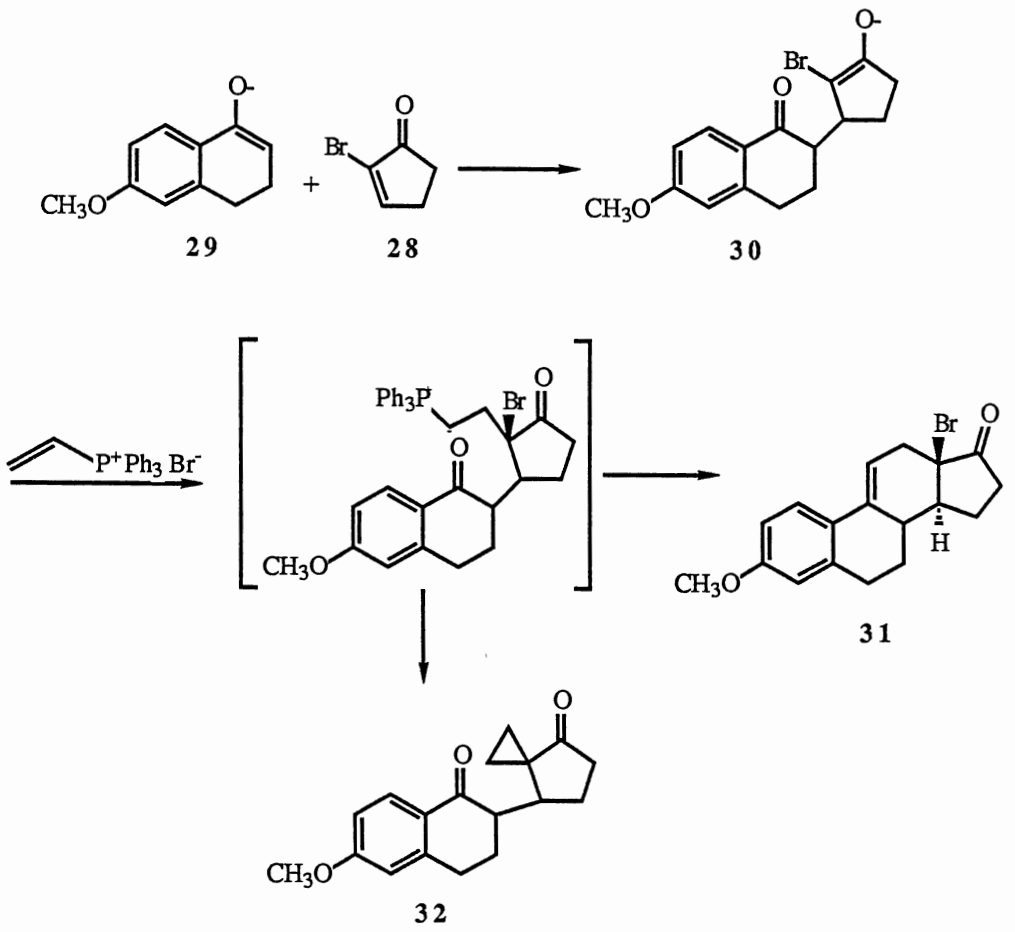
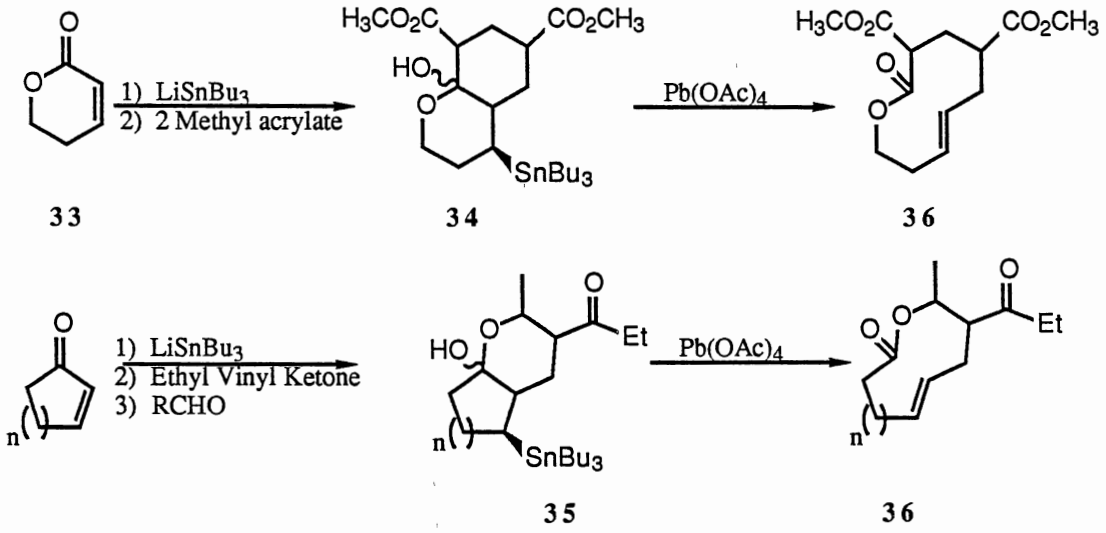


Figure 9. Synthesis of a Bromoepisterone via Tandem Michael Reactions

four tandem reactions can be accomplished in one pot. In the first paper, he used two sequential tandem reactions followed by a Wittig reaction to form (±)-9,11-dehydro-esterones.[14] These reactions were carried out sequentially in a single pot as part of a highly convergent synthesis (see Figure 9). The initial Michael adduct formed from the reaction of 2-bromo-2-cyclopentenone **28** with the enolate of 1-tetralone, **29**. This generated the enolate of bromocyclopentanone, **30**. Addition of vinyltriphenylphosphonium bromide gave the bromoestrone **31** (2-5%) and the spiro cyclopentanone **32** in 57% yield. The formation of the spiro cyclopropyl ketone was also of interest; these types of compounds

have been useful in the formation of a number of synthetic intermediates.[14] This tandem Michael-Michael ring closure, MIMIRC, involves the formation of three carbon-carbon bonds in essentially one operation, and is the shortest known total synthesis of a steroid using the connection of 10, 6, and 2 carbon fragments in one step.[14]

Posner and co-workers have also developed a procedure to use a Michael-Michael-Aldol sequence to form a variety of highly substituted cyclohexanols and macrocyclic unsaturated lactones.[15,16] These reactions involve the condensation of the enolate derived from either the unsaturated lactone **33**, or 2-cycloalkenones, with a variety of acrylates (See Figure 10) to produce the bicyclic lactols **34** and **35**. Oxidative cleavage at the



33 **34** **36**

35 **36**

Figure 10. Synthesis of Macrolides via a Michael-Michael-Aldol Sequence

hemiacetal center in **34** with lead tetraacetate then gives the unsaturated macrolides **36**. These macrolides are of interest due to their potential as antibiotic or antitumor agents. With the variety of functional groups attatched to these systems, there are many reactive sites for further synthetic manipulations to form derivatives for medicinal testing.

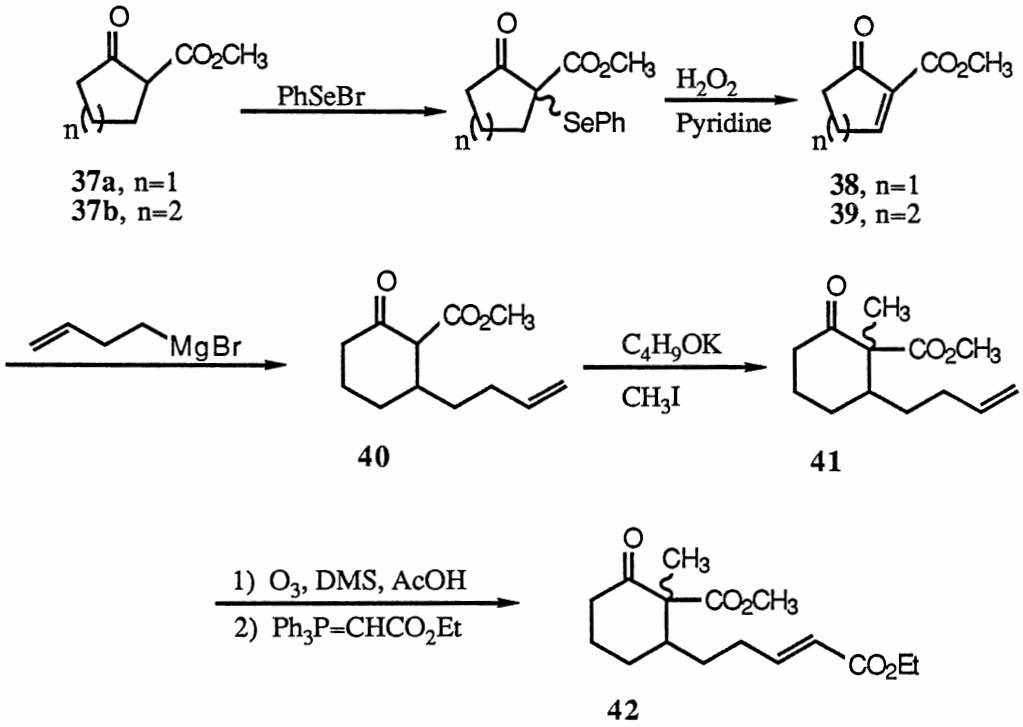
Posner has also used the a tandem Michael-aldol reaction to form a tricyclic structure containing the bicyclo[3.2.1]octane moiety.[17] These products include gibberellic acid, a plant growth stimulator; phlebiakauranol, an antibiotic; and khusimone, a fragrant norsesquiterpene.[17]

The Michael addition, and tandem reactions involving Michael additions, have proven to be quite useful in organic synthesis. Through manipulation of reaction conditions and the proper choice of both the Michael donor and acceptor, a high degree of both regio- and stereocontrol can be achieved. Posner and Kametani have shown some of the more elegant uses of these reactions to form useful natural and unnatural products. As these reactions continue to be developed, tandem reactions involving Michael processes have the potential to become an integral tool in the synthetic chemists repertoire.

CHAPTER II

DISCUSSION AND RESULTS

The synthesis of precursors for the tandem decarboxylation-Michael addition reaction under development proved to be quite difficult. The initial plan of attack was to synthesize fused five-five and six-five ring systems through a decarboxylation process followed by an intramolecular Michael addition. The synthesis of the Michael acceptor portion of the molecule proved to be quite difficult (See Figure 11). Synthesis of the β-



37a, n=1
37b, n=2

38, n=1
39, n=2

40

41

42

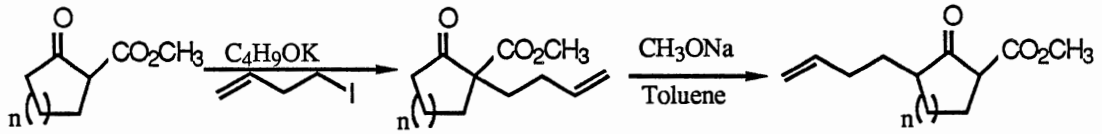
Figure 11. Synthesis of the Intramolecular Decarboxylation-Michael Addition Substrate

ketoester **37** was accomplished using Corey's synthesis.[18] To introduce the α,β-unsaturation, the selenide was formed, then oxidized and eliminated to give **38** and **39** using

an established procedure.[19] The six-membered ring system **39** was isolable, but was used in the crude state due to its instability. In the case of the five-membered ring **38**, any attempt to purify the unsaturated ketoester resulted in rapid polymerization. According to Marx and co-workers, **38** is only stable in dilute dioxane solution at -10° C.[20] This was deemed highly impractical and the synthesis of the disubstituted cyclopentanone was abandoned at this point. In the case of the six-membered ring, the conjugate addition of the Grignard reagent from 4-bromo-1-butene to **39** went smoothly and the crude product was immediately methylated to form **41**. Attempts at purifying **40** by silica gel chromatography were unsuccessful due to the enolization of the compound on the acidic silica gel. The overall yield of the 3 steps was 6%. In an attempt to improve the yields of the conjugate addition, the CuBr-dimethyl sulfide complex was added to the reaction mixture.[21] An intractable black tar was formed in the bottom of the flask. The yields were actually decreased using the cuprate, and this approach was abandoned. The ozonolysis and Wittig reaction to form **42** also gave poor yields. The inefficiency of the reaction procedure, and the difficulties in obtaining sufficient quantities for subsequent reactions indicated the need for an alternative route.

In order to circumvent some of these problems, it was decided to attempt the synthesis of bicyclic compounds through a tandem reaction process. Three different reaction sequences were attempted to synthesize the 1,6-disubstituted cycloalkanones **45** and **46**. Initially, Weiler's procedure for the alkylation of the dianion of β-keto esters was investigated.[22] Treatment of **37** with oil-free NaH, followed by *n*-butyllithium at 0° C, and then subsequent treatment with 4-bromo-1-butene, afforded none of the alkylated product. An alternative route involving a retro-Dieckmann-Dieckmann reaction sequence was then attempted[23] (See Figure 12). The 2,2-disubstituted cycloalkanones **43** and **44** were synthesized using potassium *t*-butoxide and 4-iodo-1-butene in 60% yield. The ketoester **44** was then refluxed for 8 h in xylene with fresh sodium methoxide. After an aqueous

workup, NMR analysis of the crude reaction mixture showed only the open 2-substituted dimethyl pimelate. The ketone carbonyl was no longer present.



37a, n=1
37b, n=2

43, n=1
44, n=2

45, n=1
46, n=2

Figure 12. Retro-Dieckmann-Dieckmann Reaction of 2,2-Disubstituted Cycloalkanones

In the case of the five-membered system **43** the rearrangement proved successful in (63%) using the procedure of Sisido.[24] The ketoester **45** was refluxed in fresh methanolic sodium methoxide for 10 h. The methanol was removed by distillation and replaced with toluene. The last remnants of the methanol was removed by azeotropic distillation, and the reaction was refluxed in toluene for 1 h. After an aqueous acidic work up **45** was isolated by silica gel chromatography as a clear colorless oil (63%).

An alternative alkylation procedure was used to obtain **46**. The dianion, generated by treating **37** with 2 equivalents of LDA was alkylated with 4-iodo-1-butene to give methyl 3-(3-butenyl)-2-oxocyclohexanecarboxylate (59%). The starting material **37** was recovered as the low boiling fraction during the distillation. Methylation of **46** to form **47** was found to be quite clean and proceeded in 65%. Ozonolysis of **47** to give **48**, however, proved to be quite difficult. The intermediate ozonide was resistant to standard reduction conditions-DMS and glacial acetic acid followed by washes with 1*M* HCl only partially decomposed the ozonide. After multiple washes the oil was taken up in benzene and refluxed overnight with carboethoxymethylene triphenylphosphorane. Silica gel chromatography of the product afforded the target substrate **48** in 44%. Using the procedure of Bunce, the cyclization was attempted.[25] Heating **48** in HMPA with anhydrous LiCl at 60° C for 6 h resulted in none of the expected bicyclic product. Instead,

the decarboxylation product **49** was isolated as a mixture of isomers.The isomers were assigned by analysis of their proton NMR spectra. Hickmott's study[26] of enamine alkylation gave accurate chemical shift and coupling constant data for a variety of 2,6-disubstituted cyclohexanones related to **49**. The signals assigned to the methyl protons were used for the determination of isomeric ratios. The trans isomer (J = 7 Hz), was found to be more upfield than in the cis (J = 6.0 Hz), by approximately 0.10 ppm. Using these values, the stereochemistry of the isolated de-carboxylation product was assigned. At 60°C the crude NMR showed that the trans isomer was present in 64% , while at 90°C the cis isomer predominated at 66%, and at 120°C the thermodynamically more stable cis isomer

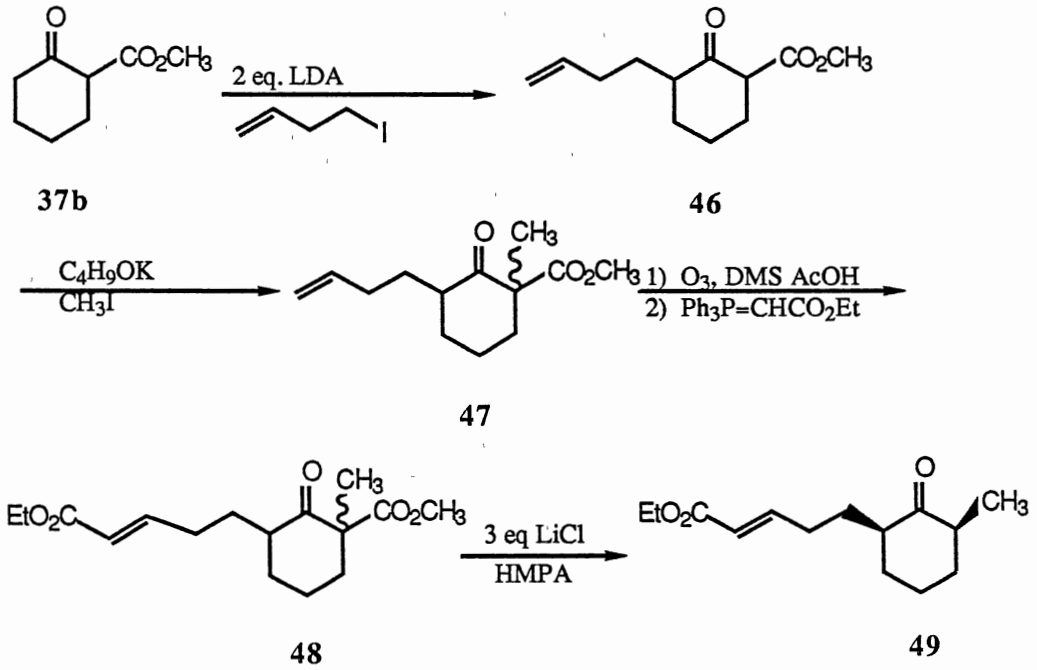


Figure 13. Initial Scheme for the Synthesis of Bicyclo[3.3.1]Nonan-8-ones

was present in excess of 90%. The cis isomer was expected to be the predominant isomer from the decarboxylation; in this configuration both of the substituents can be found equatorial in the chair conformation, thus alleviating any diaxial interactions.

There are two possible reasons to account for the failure of **48** to cyclize. Either the chain containing the Michael acceptor was not long enough or the anion generated was not sufficiently stable. When the cyclization occurs in the case of the five-membered ring, a bicyclo[3.2.1]octan-8-one results, while the six-membered ring forms a bicyclo[3.3.1]-nonan-8-one. Both ring systems are well documented.[27-29] To stabilize the anion produced by decarboxylation a second ester group was introduced α to the existing methyl ester (See Figure 14). By using an established procedure, the magnesium enolates of **45** and **46** were alkylated preferentially at the C-1position to form **50** and **51**, respectively.[30]

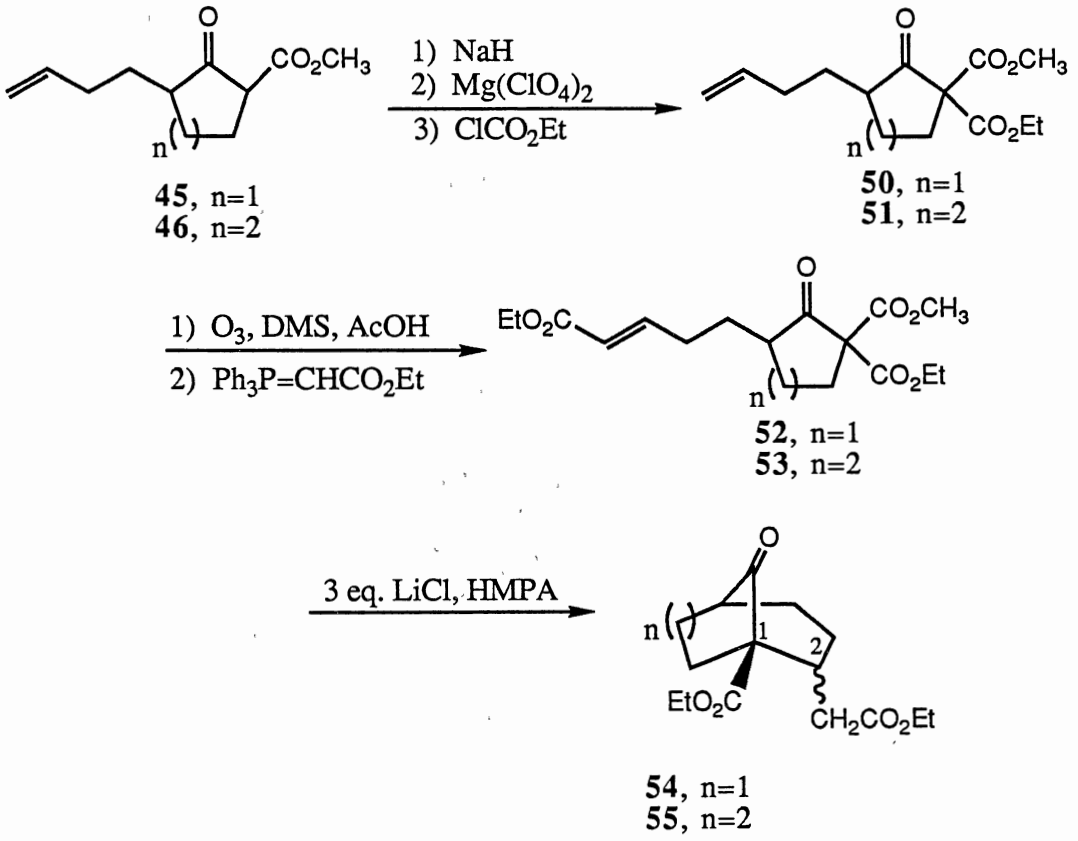


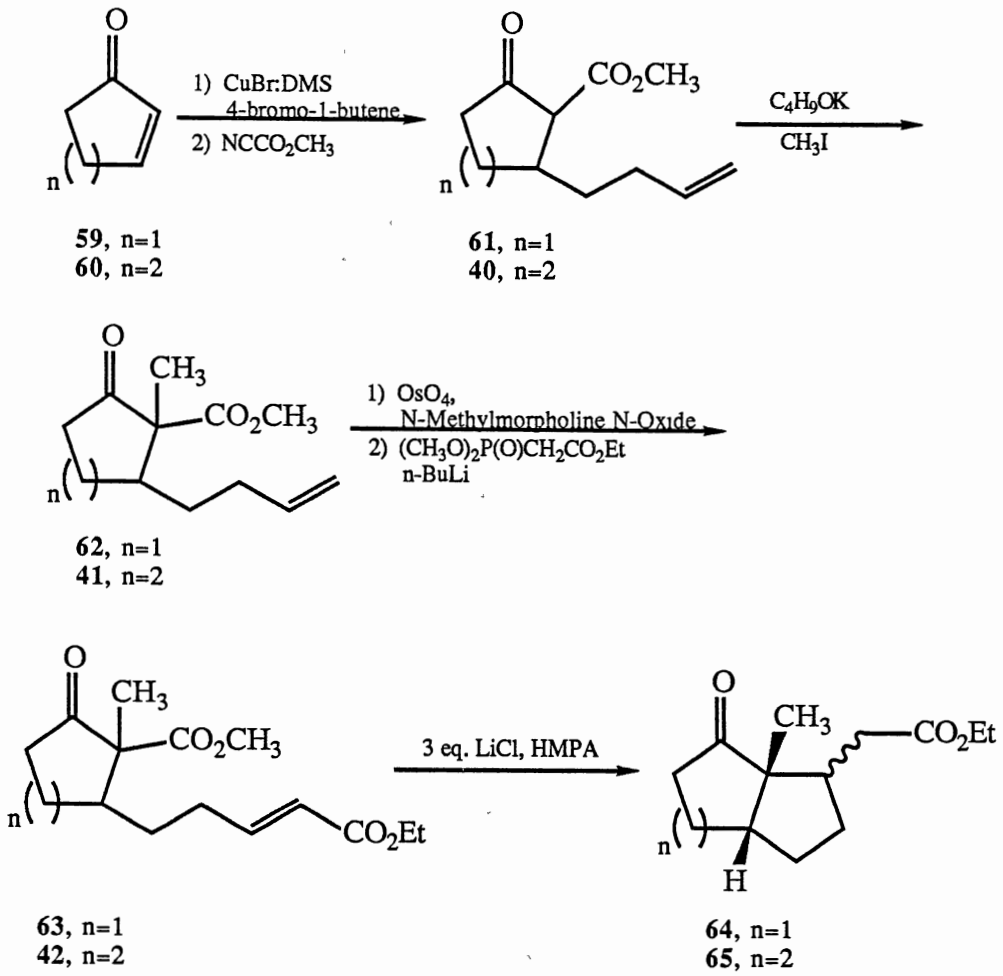
Fig 14. Synthetic Scheme for the Cyclization of Triesters **52** and **53**

Once again the ozonolysis and Wittig reactions proceeded in very modest yields. The ozonide did not decompose even after stirring with activated zinc and glacial acetic acid. Another problem encountered was that the resulting triesters **52** and **53** did not elute from

the silica gel filter pad following Wittig olefination. As the solvent polarity was increased, both the triphenylphosphine oxide and the triesters eluted at the same time. In an alternative procedure the aldehyde was treated with the Wadsworth-Emmons reagent generated from ethyl dimethylphosphono-acetate.[31] Although the phosphorus by-product was removed in the aqueous workup, only modest yields of **52** and **53** were realized. A small amount of the triesters **52** and **53** have been cyclized using lithium chloride in HMPA (125° C for 6 h). Although there are three new chiral centers formed, two of them have restricted configurations because they are at the bridgeheads. The stereochemistry at C-2 in the resulting bicyclic octanone **54** and in the nonanone **55** has yet to be determined. It is expected that the methylene group will be pseudoequatorial to diminish any diaxial interactions. Separation of the mixture has proven to be quite difficult. Both ^{1}H and ^{13}C NMR spectra have confirmed the cyclization to the bicyclic skeleton. In the proton spectra, signals for the olefinic protons are absent in both cases. In the ^{13}C spectra, the ketone carbonyl, seen at approximately 208 ppm, has been shifted downfield in both cases to approximately 220 ppm. This is in agreement with values found in the literature for the bicyclic ketone structures. According to Heumann[27-29] the carbonyl found in bicyclo-[3.2.1]octan-8-ones and bicyclo[3.3.1]nonan-9-ones appear in the range of 214-223 ppm depending upon the substituents on the molecule. Although the cyclization was successful in both cases, syntheses of the triesters **52** and **53** were found to be difficult. In order for this process to become synthetically useful, alterna-tive schemes must be found.

ALTERNATIVE SYNTHETIC SCHEMES

There are numerous ways to synthesize the starting materials for these studies. One synthetic approach would form the fused ring systems by starting with the conjugate addition to **59** and **60**. This would circumvent the instability of **40** and **41**. By trapping the intermediate enolate with ethyl cyanoformate, the desired β-ketoesters **61** and **40** would be formed regioselectively.[32] Finding a procedure that gives acceptable yields for



59, n=1
60, n=2

61, n=1
40, n=2

62, n=1
41, n=2

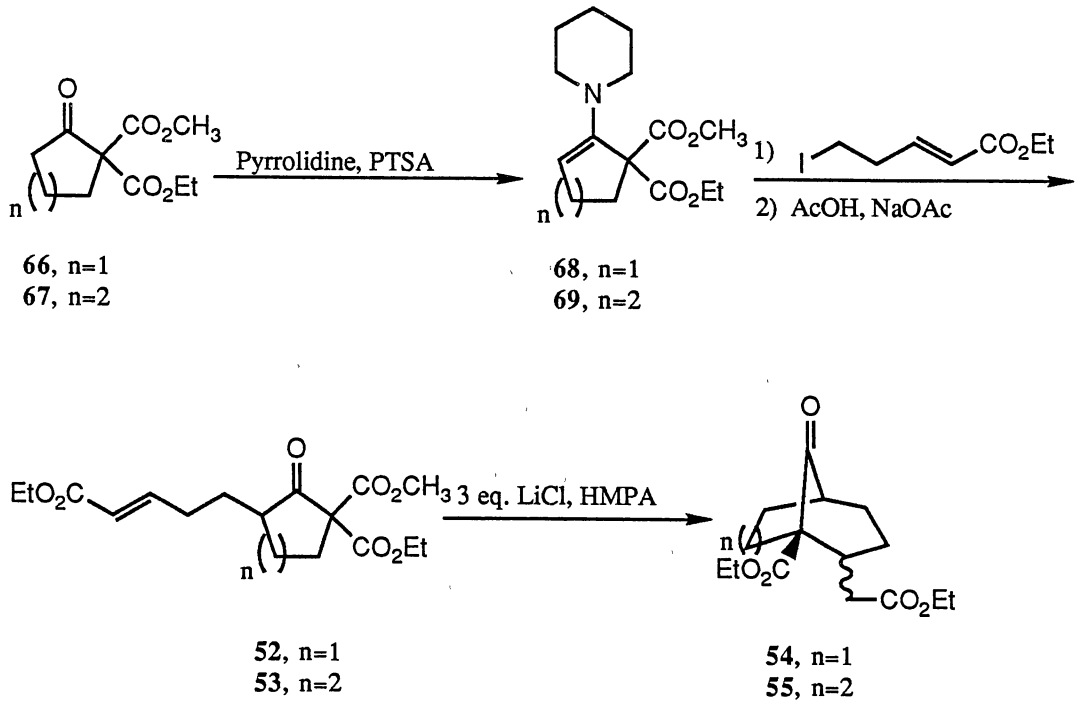
63, n=1
42, n=2

64, n=1
65, n=2

Figure 15. An Alternative Route to the Fused Bicyclic Systems

the ozonolysis is vital to make this reaction sequence viable, however using osmium tetroxide and N-methylmorpholine N-oxide would circumvent the difficulties encountered in the ozonolysis-Wittig sequence. If only the decarboxylation occurs, then the methyl group could be replaced with an ethyl ester using the magnesium enolate to increase the stability of the anion and allow the cyclization to proceed smoothly to form **64** and **65**.

In the proposed alternative route to the bicyclic systems (Figure 16), many of the stumbling blocks found in the attempted synthesis may be avoided. The selective alkylation at C-3 could be accomplished by one of two methods. Treating the enamines **68** and



66, n=1
67, n=2

68, n=1
69, n=2

52, n=1
53, n=2

54, n=1
55, n=2

Figure 16. An Alternative Route to the Bicyclic Systems

69 with ethyl 5-iodo-2-pentenoate followed by hydrolysis to give the corresponding ketone, should give the desired triesters **52** and **53**. If this reaction failed, a Michael addition of **68** and **69** with acrolein[33] could also be used to alkylate at the C-3 position. Treatment of the resulting aldehydes with the Wadsworth-Emmons reagent should give the desired ring closure substrates **52** and **53** in good yields, and the closure to the desired bicyclic products should proceed smoothly. This sequence is shorter than those previously described and uses well established procedures. It also eliminates the ozonolysis which has been a limiting step in the sequences.

Although the tandem decarboxylation-Michael addition was successful, the overall reaction sequence to the triesters **52** and **53** resulted in modest yields at best. The sequence was plagued by low yields and difficult separations. Cyclization to the bicyclic products **54** and **55** was successful, also in modest yields. If this scheme is ever to be developed as a useful synthetic tool, all of the obstacles must be overcome. When, and if,

this is accomplished, this method could be useful in the synthesis of natural and unnatural products containing the fused and the bicyclic systems that can be formed by this method.

CHAPTER III

EXPERIMENTAL

General Experimental Methods. All experiments were carried out in flame dried glassware under an atmosphere of dry nitrogen. *tert*-Butyl alcohol was distilled from calcium hydride under nitrogen. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen. All reagents were used as recieved from either Aldrich or Lancaster unless otherwise noted. The molarity of the *n*-butyllithium was checked using the diphenylacetic acid method.[34]

Nuclear magnetic resonance spectra were obtained on a Varian XL-VXR-300 superconducting FT instrument, with ^{1}H and ^{13}C spectra recorded at 300 and 75 MHz, respectively. Samples were prepared in $CDCl_3$ and are reported in ppm downfield from TMS. Infrared spectra were recorded on a PE-681 spectrometer as a thin film on NaCl plates and are reported in cm^{-1}. High resolution mass spectral data was obtained at 70 eV on a VG-ZAB-2SE mass spectrometer.

General Workup Procedure. The reaction mixture was poured into a separatory funnel containing 100 mL of 1 *M* HCl and extracted 3 times with 75-mL portions of ether. The combined ether layers were then washed with 100-mL portions of saturated $NaHCO_3$, 5% sodium thiosulfate, and saturated NaCl solutions. The ether layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation under an aspirator vacuum.

General Procedure for Generating Lithium Diisopropylamide (LDA). LDA was generated using the following procedure. The diisopropylamine was dissolved

in THF and cooled to -78° C. To this stirring solution, 1.1 eq. of *n*-butyllithium was added dropwise via a syringe and allowed to stir for 20 min. A THF solution of the ketone was then added dropwise from an addition funnel. The solution was stirred for another 20 min at -78° C to generate the anion. The anion was quenched by adding a THF solution of the alkylating agent.

Methyl 2-Oxocyclohexanecarboxylate (37). The procedure of Corey and coworkers[18] was used. In a 2-L 3-necked round-bottomed flask equipped with a condenser, dropping funnel, and mechanical stirrer, 15.28 g (0.6378 moles) of oil-free NaH was suspended in 300 mL of 1,4-dioxane and 134 mL (143.41 g, 1.60 moles) of dimethylcarbonate was added. The solution was warmed on an oil bath maintaining the temperature between 80-85° C. In the dropping funnel, 33 mL (31.25 g 0.3184 moles) of cyclohexanone was diluted with 100 mL of dioxane and added dropwise over 3 h. A brown solid mass was formed in the flask. The solution was heated for an additional 3 h during which time most of the solid was redissolved. The oil bath was removed and the reaction was allowed to stir for an additional 2 h. The flask was lowered into an ice bath and cooled to 0° C. A solution of 40 mL of glacial acetic acid in 30 mL of water was added dropwise and stirred for 30 min. This mixture was poured into a 1-L round-bottomed flask and the solvent removed by rotary evaporation. The concentrated solution was diluted with 500 mL of water and extracted with 100-mL of ether (3x). The combined ether layers were washed with 150-mL portions of saturated aqueous $NaHCO_3$ (1x), water (1x), and brine solutions (1x) and dried over anhydrous $MgSO_4$. The ether solution was concentrated to an orange oil and fractionally distilled under vacuum to yield 37.8 g (0.24 moles, 76 %) of **37** as a clear oil that is 95% pure, bp 46° C (0.10 mm Hg) . ^{1}H NMR δ 3.75 (s, 3 H); 2.3 (m, 5 H); 1.6 (m, 4 H); ^{13}C NMR δ 173.1, 172.1, 97.6, 51.3, 41.5, 29.0, 27.1, 22.4, 21.9.

Methyl 2-Oxo-1-phenylselenocyclohexanecarboxylate. Using the procedure of Reich and coworkers,[19] LDA was generated on a 15.4 mmole scale in a 100-

mL 3-necked round-bottomed flask using the standard procedure. A 15-mL THF solution containing 2.00 g (12.8 mmoles) of **37** was added dropwise from the dropping funnel during 10 min and then stirred for 20 min. In the dropping funnel, 2.41 g (7.7 mmoles) of diphenyl diselenide was dissolved in 15 mL of THF and 1.30 g (7.7 mmoles) of Br_2 was added. The resulting phenylselenyl bromide was added dropwise to the reaction mixture during 5 min.

The reaction mixture was stirred for 20 min, then poured into a separatory funnel containing 75 mL of 0.5 *M* HCl and 100 mL of 1:1 ether:hexane. This was separated and the ether layer was washed with 100-mL portions of water, saturated aqueous $NaHCO_3$, and brine. The ether solution was dried over $MgSO_4$ and concentrated to yield an orange oil. The oil was chromatographed over silica gel eluting the first band with hexane to afford unreacted diphenyl diselenide. The polarity of the eluent was increased to 5% ether in hexane and the selenide was eluted to yield 2.64 g (8.5 mmoles, 66%) as a pale yellow oil. ^{1}H NMR δ 7.5-7.2 (m, 5 H), 3.7 (s, 3 H), 2.65 (m, 1 H), 2.4 (m, 3 H), 2.0-1.4 (m, 4 H); ^{13}C NMR δ 203.9, 169.5, 138.3, 129.5, 128.7, 125.7, 62.5, 52.8, 40.9, 37.9, 26.9, 23.6; IR (thin film) 3065, 2950, 2875, 1735, 1715, 1580, 740, 700 cm^{-1}.

Methyl 6-Oxo-1-cylohexenecarboxylate (39). The procedure of Reich and coworkers was employed.[19] In a 250-mL 3-necked round-bottomed flask 2.64 g (8.50 mmoles) of the selenide was dissolved in 50 mL of CH_2Cl_2 and 1.34 g (16.9 mmoles) of pyridine was added. The reaction was cooled to 0° C and a solution of 2.60 g of 30% H_2O_2 in 5 mL of H_2O was added slowly to the vigorously stirred mixture. The cold bath was removed and the system was allowed to warm to room temperature. The yellow solution darkened and then quickly lightened indicating the reaction was complete. The crude reaction mixture was poured into a separatory funnel containing 50 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 50 mL of CH_2Cl_2. The combined organic layers were washed with 100-mL portions of 1 *M* HCl and brine, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* yielding 1.23 g (7.99

mmoles, 94%) of **39** as a yellow oil that was used immediately without further purification. ^{1}H NMR δ 7.71 (t, 1 H, J = 4.3 Hz), 3.8 (s, 3 H), 2.6-1.7 (cplx, 6 H); ^{13}C NMR δ 194.4, 165.2, 156.5, 132.9, 52.1, 38.6, 26.1, 22.1.

Methyl 6-(3-Butenyl)-2-oxocyclohexanecarboxylate (40). In a 100-mL 3-necked round-bottomed flask equipped with a magnetic stirrer, a condenser, and a dropping funnel 0.25 g (10.4 mmoles) of freshly crushed Mg turnings were flamed dried under a stream of dry nitrogen. The turnings were covered with 5 mL of anhydrous ether and a few drops of 4-bromo-1-butene were added to initiate formation of the Grignard reagent. As the reaction started, the remaining 1.40 g (10.4 mmoles) of the bromide in 5 mL of ether was added dropwise at a rate sufficient to keep the reaction refluxing. The reaction mixture was then refluxed for 1 h. At the end of the reflux period, a Gilman's test[35] was performed to insure that the Grignard reagent was formed. A 10-mL ether solution containing 1.20 g (7.8 mmoles) of **39** was added dropwise, with the formation of a yellow solid as the enone came in contact with the reaction mixture. The reaction was stirred for 30 min at room temperature. The reaction was quenched with 10 mL of saturated NH_4Cl and the general workup was used substituting saturated NH_4Cl solution for the 1 *M* HCl. After concentration of the ether solution 1.56 g (7.4 mmoles, 95%) of **40** was obtained as a pale yellow oil. This was used without further purification. ^{1}H NMR δ 5.8 (cplx, 1 H), 5.0 (cplx, 2 H), 3.8 (s, 3 H), 3.19 (d, 1 H, J = 11.0 Hz), 2.6-1.2 (cplx, 11 H); ^{13}C NMR δ 207.2, 174.7, 138.2, 114.8, 97.6, 57.8, 52.7, 48.7, 37.8, 31.1, 28.0, 20.0; IR (thin film) 3060, 2840, 1740, 1710, 990, 905 cm^{-1}.

Methyl 2-(3-Butenyl)-1-methyl-6-oxocyclohexanecarboxylate (41). In a 50-mL 3-necked round-bottomed flask, a mixture of 20 mL of dry *tert*butyl alcohol and 0.20 g (5.10 mmoles) of potassium was refluxed until all of the metal had dissolved. The clear yellow solution was cooled to room temperature and a 5-mL *tert*-butyl alcohol solution of 1.00 g (4.80 mmoles) of **40** was added dropwise. The solution was stirred for 1 h and turned a deep red color. A 3-mL *tert*-butyl alcohol solution of 0.68 g (4.80

mmoles) of methyl iodide was slowly added and mixture was refluxed overnight. The standard workup yielded a pale yellow oil. This was chromatographed on silica gel with 500-mL portions of hexane followed by 3%, 7%, and 10% ether in hexane where 0.23 g (1.0 mmoles) of **40** eluted as a pale yellow oil. ^{1}H NMR δ 5.8 (cplx, 1 H), 5.0, (dd, 2 H, J = 6.9, 14.2 Hz), 3.7 (s 3 H), 2.7 (m, 1 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 1.8-1.4 (cplx, 8 H), 1.39 (s, 3 H); ^{13}C 208.0, 171.8, 138.1, 115.0, 60.8, 51.9, 48.1, 39.9, 32.4, 30.1, 26.6, 25.3, 18.6. IR (thin film) 3060, 2940, 2855, 1740, 1638, 1445, 1200, 910 cm^{-1}

Methyl 2-(4-Ethoxycarbonyl-3-butenyl)-1-methyl-6-oxocyclohexane-carboxylate (42). In a 250-mL round-bottomed flask, 0.56 g (2.50 mmoles) of keto-ester **41** was dissolved in 75 mL of methanol and cooled to -78° C. Ozone was bubbled through the reaction mixture for 15 min. At the end of the reaction time approximately 1 mL of dimethyl sulfide was added, followed by 1 mL of glacial acetic acid to decompose the ozonide. The methanol was removed by rotary evaporation at greater than 45°C. The resulting solution was diluted with 100 mL of water and extracted with 75-mL of ether (3x). The combined ether layers were washed with 100 mL of saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated to give 0.55 g of a pale yellow oil that was used without further purification. The aldehyde was dissolved in 100 mL of benzene in a 250 mL round-bottomed flask, 0.84 g (2.40 mmoles) of ethoxycarbonyl-methylene triphenylphosphorane was added, and the solution refluxed overnight. The reaction was cooled and concentrated to give a cream colored solid. This was filtered through a silica pad using 5% ether in hexane until the first traces of triphenylphosphine oxide were noted after evaporation of the solvent. The resulting pale yellow oil weighing (0.35 g) was separated on a 20 cm X 20 cm preparative thick layer silica gel plate eluting once with hexane, twice with 3% ether in hexane, twice with 5% ether in hexane, and twice with 10% ether in hexane. The band with the lowest R_f afforded 0.180 g (0.60 mmoles, 25%) of **41** as a pale yellow oil. ^{1}H NMR δ 6.92 (dt, 1 H, J = 7.8, 15.7 Hz), 5.86 (d, 1 H, J = 15.6 Hz), 4.17 (q, 2 H, J = 7.4 Hz), 3.69 (s, 3 H), 2.65 (m, 2 H), 2.45 (m, 2 H),

2.09 (m, 2 H), 1.8 (m, 3 H), 1.7 (m, 2 H), 1.35 (s, 3 H), 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 207.3, 171.6, 166.3, 148.1, 121.7, 60.7, 60.1, 51.9, 48.3, 39.7, 30.8, 29.3, 26.6, 25.1, 18.6, 14.1; IR (thin film) 2950, 2875,1740, 1655, 985 cm^{-1}; MS m/e 296 (0.70), 268 (9.3), 236 (11.4), 222 (16.1), 208 (20.2), 191 (51.4), 162 (29.3), 150 (25.4), 137 (44.0), 114 (44.9), 95 (64.1), 81 (100.0), 67 (50.6), 55 (83.0).

Methyl 1-(3-Butenyl)-2-oxocyclohexanecarboxylate (44). In a 250-mL 3-necked round-bottomed flask equipped with a magnetic stirrer, a condenser, and a dropping funnel, 50 mL of dry *tert*-butyl alcohol containing 1.88 g (48.0 mmoles) of potassium were refluxed until all of the metal had dissolved. The solution was cooled to room temperature, and a 20-mL *tert*-butyl alcohol solution of 5.00 g (38.4 mmoles) of **37b** was added dropwise over 10 min. This solution was stirred for 20 min at room temperature to generate the anion, and a 10-mL solution of 5.18 g. (38.4 mmoles) of 4-bromo-1-butene in *tert*-butyl alcohol was added dropwise over 10 min. The solution was refluxed for 10 h. After cooling to room temperature, the general work up procedure resulted in a pale yellow oil which was distilled under vacuum through a 15-cm Vigreaux column to afford 4.00 g (19.0 mmoles, 60%) of **44**, bp 55° C (0.10 mm Hg). ^1H NMR δ 5.8 (m, 1 H), 5.0 (dd, 2 H, J = 1.8, 17.1 Hz), 3.74 (s, 3 H), 2.6-2.4 (cplx, 3 H), 2.0-1.9 (cplx, 4 H), 1.5-1.4 (cplx, 1 H); ^{13}C NMR δ, 207.6, 172.3, 137.8, 114.7, 60.5, 52.1, 41.0, 36.0, 33.8, 28.5, 27.5, 22.4; IR (thin film), 3085, 2860, 1740, 1715, 1640, 1450, 1205, 1010 cm^{-1}; HRMS, exact mass calculated for $C_{12}H_{18}O_3$, *m/e* 210.2748, found *m/e* 211.1264 (M+1).

Methyl 1-(3-Butenyl)-2-oxocyclopentanecarboxylate (43). The alkylation was carried out as in **44**, using 3.03 g (77.5 mmoles) of potassium metal, 10.00 g (70.5 mmoles) of **37a** and 14.00 g (77.5 mmoles) of 4-iodo-1-butene. Vacuum distillation at 75° C (0.10 mm Hg) afforded 11.86 g (60.4 mmoles, 86%) of **43** as a clear colorless oil. ^1H NMR δ 5.78 (m, 1 H), 5.00 (dt, 2 H, J = 1.6, 6.0 Hz), 3.71 (s, 3 H) 2.6-2.2 (cplx, 3 H), 2.2-1.9 (cplx, 6 H), 1.7 (m, 1 H); ^{13}C NMR δ 214.4, 171.1, 137.3, 114.9, 59.6, 52.3, 37.7, 32.9, 32.6, 28.9, 19.4; IR (thin film) 3070, 2950, 1750, 1730,

1640, 1405, 1300-1100, 910 cm^{-1}; HRMS, exact mass calculated for $C_{11}H_{16}O_3$ *m/e* 196.2471, found *m/e* 196.1099.

4-Iodo-1-butene. In a 500-mL round-bottomed flask, 20.0 g (0.15 moles) of 4-bromo-1-butene and 66.6 g (0.44 moles) of NaI were dissolved in 300 mL of acetone. This solution was refluxed for 10 h and allowed to cool to room temperature. The crude reaction mixture was poured into 500 mL of water and extracted 3 times with 125-mL portions of ether. The combined ether layers were washed twice with 200-mL portions of 5% $Na_2S_2O_3$ and 200 mL of saturated aqueous NaCl. The ether solution was dried with anhydrous $MgSO_4$ and the ether was removed by distillation at ambient pressure. The iodide was isolated by vacuum distillation (70°C, 10 mm Hg). The reciever was cooled in a dry ice/acetone bath, and the iodide collected as a volatile orange liquid weighing 24.9 g (0.14 moles, 92%). ^1H NMR δ 5.7 (m, 1 H), 5.08 (dd, 2 H, J = 1.5, 11.5 Hz), 3.17 (t, 2 H, J = 7.2 Hz), 2.60 (dt, 2 H, J = 1.5, 7.0 Hz); ^{13}C NMR δ 137.2, 117.4, 38.0, 5.1; IR (thin film) 3080, 1945, 1250, 995, 925.cm^{-1}

Methyl 3-(3-Butenyl)-2-oxocyclopentanecarboxylate (45). The method of Sisido and coworkers[24] was used. In a 250-mL 3-necked round-bottomed flask equipped with a magnetic stirring bar, a condenser, a dropping funnel, and a glass stopper 1.13 g (48.9 mmoles) of sodium metal was dissolved in 50 mL of methanol. To the resulting sodium methoxide, a 20-mL ethanol solution containing 8.00 g (40.8 mmoles) of **43** was added dropwise during 20 min resulting in a pale green solution. The reaction was refluxed for 8 h, at which time the methanol distilled until about 10 mL of methanol remained. To the reaction mixture, 150 mL of toluene was added and the remaining methanol azeotroped until the head temperature reached 110° C. The toluene solution was refluxed for 1 h. After cooling to room temperature, the reaction mixture was diluted with 100 mL of 10% acetic acid and extracted with 75-mL of ether (3x). The combined ether layers were washed with 200-mL portions of saturated Na_2CO_3 (2x), 200 mL of saturated NaCl (1x), dried over anhydrous $MgSO_4$, and concentrated. The resulting oil was

chromatographed on silica gel eluted with 5% ether in hexane to give 5.30 g (27.0 mmoles, 66%) of **45** as a clear colorless oil. ^{1}H NMR δ 5.8 (m, 1 H), 5.0 (m, 2 H), 3.75 (s, 3 H), 3.3 (m, 0.5 H), 3.2 (m, 0.5 H), 2.5-1.5 (cplx, 9 H); ^{13}C NMR δ, 212.9, 169.9, 137.6, 115.3, 54.8, 53.9, 52.3, 51.4, 51.4, 48.6, 48.1, 44.5, 33.7, 31.6, 31.3, 29.0, 28.6, 27.2, 25.0, 25.0, 22.6; HRMS, exact mass calculated for $C_{11}H_{16}O_3$ *m/e* 196.2471, found *m/e* 196.1097.

Methyl 3-(3-Butenyl)-2-oxocyclohexanecarboxylate (46). In a 250-mL 3-necked round-bottomed flask equipped with a magnetic stirrer, a condenser, a dropping funnel, and a rubber septum, LDA was generated on a 20 mmole scale using 2.03 g of diisopropylamine and 20.0 mL of 1.0 *M* *n*-butyllithium. In the dropping funnel a 5-mL THF solution containing 1.56 g (10.0 mmoles) of **37** was added dropwise and stirred for 30 min at 0°C to generate the dianion. A 5-mL solution of THF containing 2.00 g (11.0 mmoles) of **7** was added dropwise and stirred for 30 min. The general workup procedure afforded a pale yellow orange oil that was distilled under vacuum to give 1.25 g (5.94 mmoles, 59%) of **46** at 80-85° C (0.10 mm Hg). ^{1}H NMR δ 5.8 (m, 1 H), 5.0 (m, 2 H), 3.76 (s, 3 H), 2.6-1.2 (cplx, 12 H); ^{13}C NMR δ 207.2, 174.7, 138.4, 138.1, 114.8, 114.7, 57.8, 55.9, 52.2, 51.9, 51.3, 50.0, 48.6, 37.8, 34.9, 31.1, 31.0, 30.8, 28.0, 27.0, 24.1, 20.0; IR (thin film) 2925, 2850, 1740, 1710, 1650, 1610, 1450, 995, 910 cm^{-1}; HRMS, exact mass calculated for $C_{12}H_{18}O_3$, *m/e* 210.2748, found *m/e* 211.0300, (M+1)

Methyl 3-(3-Butenyl)-1-methyl-2-oxocyclohexanecarboxylate (47). In a 100-mL 3-necked round-bottomed flask equipped with a stirring bar, a condenser, and a dropping funnel 0.46 g (19.0 mmoles) of oil-free NaH was suspended in 25 mL of dry THF. A 10-mL solution of THF containing 3.35 g (15.9 mmoles) of **46** was added dropwise and stirred for 10 min to give a yellow solution. In the dropping funnel, a 10-mL THF solution containing 2.71 g (19.1 mmoles) of methyl iodide was added dropwise and the reaction mixture was refluxed overnight. After cooling to room temperature, the

general workup procedure yielded a pale yellow oil that was chromatographed on a 60 cm silica gel column using hexane, 3% ether, 5% ether, and 10% ether in hexane solutions to give 2.31 g (10.3 mmoles, 65%) of **47** as a clear colorless oil. ^{1}H NMR δ 5.8 (m, 1 H), 4.90 (dd, 2 H, J = 1.7, 16.4 Hz), 3.71 (s, 3 H), 2.6-2.3 (cplx, 2 H), 2.2-1.9 (cplx, 5 H), 1.8-1.5 (cplx, 3 H), 1.27 (s, 3 H); ^{13}C NMR δ 208.6, 173.6, 138.4, 114.6, 57.2, 52.2, 48.7, 38.9, 34.9, 31.1, 28.4, 22.8, 21.4; IR (thin film) 3060, 2920, 2850, 1740, 1710, 1635, 1450, 900 cm^{-1}.

Methyl 3-(4-Ethoxycarbonyl-3-butenyl)-1-methyl-2-oxocyclohexane-carboxylate (48). In a 500-mL 3-necked round-bottomed flask, 4.00 g (17.8 mmoles) of **47** was dissolved in 250 mL of methanol and cooled to -78° C. Ozone was bubbled through the solution for 40 min. A solution of 3-mL of dimethyl sulfide and 2 mL of glacial acetic acid was added, and the methanol removed by rotary evaporation. The resulting oil was taken up in 100 mL of 1 *M* HCl and stirred for 2.5 h with zinc dust[3]. This solution was extracted 3 times with 100-mL portions of ether and the combined ether layers were washed with 100-mL portions of 1 *M* HCl (2x), 100 mL of $NaHCO_3$ (1x), and 100 mL of saturated NaCl (1x), dried over anhydrous $MgSO_4$, and concentrated. The aldehyde was immediately dissolved in 200 mL of benzene, 5.24 g (13.7 mmoles) of carboethoxymethylene triphenylphosphorane was added and the reaction refluxed for 10 h. The reaction was cooled and the solvent removed by rotary evaporation. The resulting yellow viscous oil was filtered through a pad of silica gel with 10% ether in hexane until the first traces of triphenylphosphine oxide were seen upon removal of the solvent. This clear oil was chromatographed on silica gel with hexane gradually increasing the polarity with ether to a maximum of 20%. The second band contained **48** as a clear colorless oil weighing 2.30 g (7.80 mmoles, 44%). ^{1}H NMR δ 6.9 (dt, 1 H, J = 7.0, 15.6 Hz), 5.8 (d, 1 H, J = 15.6 Hz), 4.2 (q, 2 H, J =7.1 Hz), 3.7 (s, 3 H), 2.6-2.1 (cplx, 5 H), 2.1 (m, 2 H), 1.8 (m, 2 H), 1.3 (cplx, 8 H); ^{13}C NMR δ 208.3, 173.5, 166.5, 148.7, 121.6, 60.5, 57.3, 52.4, 48.5, 39.0, 35.1, 29.6, 27.8, 22.8, 21.3, 14.2; IR (thin film) 2965,

2920, 2850, 1740, 1720, 1705, 1645, 1440, 1360, 1150, 1130, 1040 cm^{-1}; HRMS, exact mass calculated for $C_{16}H_{24}O_5$, *m/e* 296.3646, found *m/e*, 297.1501, (m+1).

Ethyl *cis*-5-(3-Methyl-2-oxocyclohexyl)-2-pentenoate (49). The procedure of Bunce and coworkers[25] was used. In a 15-mL round-bottomed flask 0.50 g (1.7 mmoles) of **48** was dissolved in 4 mL of hexamethylphosphoramide (HMPA) and 0.22 g (5.1 mmoles) of anhydrous LiCl was added. This solution was heated to 90° C and stirred for 6 h. The solution was poured into 30 mL of 1 *M* HCl and extracted 3 times with 15-mL portions of ether. The combined ether solutions were washed with 50-mL portions of saturated $NaHCO_3$, saturated NaCl solutions, and dried with anhydrous $MgSO_4$. The ether was removed by rotary evaporation and the resulting oil chromatographed on one 20 cm x 20 cm thick layer silica gel plate (Analtech No.) eluting with hexane (1x), 3% ether in hexane (2x), and 5% ether in hexane (3x). There were 3 major bands noted on the plate with the middle band containg 60 mg of **49**. ^1H NMR δ 6.95 (dt, 1 H, J = 15.7, 7.3 Hz), 5.80 (d, 1 H, J = 15.7 Hz), 4.2 (q, 2 H, J=7.1 Hz), 2.6-1.5 (cplx, 9 H), 1.4-1.1 (cplx, 6 H), 1.0 (t, 3 H, J=6.5 Hz); ^{13}C NMR δ 213.6, 166.6, 148.9, 121.4, 60.1, 49.7, 45.6, 37.3, 35.2, 29.8, 27.6, 25.5, 14.4, 14.2; IR (thin film) 2920, 2845, 1720, 1710, 1650, 1450, 1050 cm^{-1}.

Ethyl Methyl 3-(3-Butenyl)-2-oxocyclopentane-1,1-dicarboxylate (50). The procedure of Ferris and coworkers[30] was used. A 250 mL 3-necked round-bottomed flask equipped with a condensor, a dropping funnel, and a glass stopper was charged with 0.72 g. (30.0 mmoles) of oil-free NaH and 25 mL of dry THF. To this suspension a 20-mL THF solution containing 5.30 g (27.0 mmoles) of **45** was added dropwise to form a yellow solution. After stirring for 10 min, 6.70 g (30.0 mmoles) of $Mg(ClO_4)_2$ was added in a single portion and stirred until all of the perchlorate was dissolved. A 15-mL THF solution of 3.04 g (28.0 mmoles) of ethyl chloroformate was added dropwise and then refluxed for 30 min. The reaction was cooled, and diluted with 150 mL of 1 *M* H_2SO_4 and extracted with 75-mL of ether (2x). The combined ether

solutions were washed with 100-mL of saturated aqueous $NaHCO_3$ (1x) and saturated aqueous NaCl (1x). The ether solution was dried over anhydrous $MgSO_4$ and concentrated. The resulting pale yellow oil was distilled under vacuum collecting 5.42 g (20.2 mmoles, 75 %), bp 120-126° C (0.10 mm Hg) of **50** as a mixture of diastereomers. ^1H NMR δ 5.8 (m, 1 H), 5.0 (dt, 2 H, J = 1.5, 10.3 Hz), 4.3 (q, 2 H, J = 7.2 Hz), 3.8 (s, 3 H), 2.8-2.5 (cplx, 1 H), 2.5-1.8 (cplx, 6H), 1.7-1.4 (cplx, 2 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 208.1, 167.5, 167.3, 167.0, 166.8, 137.4, 115.4, 68.1, 68.0, 62.2, 62.2, 53.1, 48.1, 31.3, 30.8, 30.7, 29.4, 29.4, 26.2, 26.1, 13.8; IR (thin film), 3060, 2920, 1765, 1755, 1740, 1720, 1710, 1635, 910, 725, 640 cm^{-1}; HRMS, exact mass calculated for $C_{14}H_{20}O_5$, *m/e* 268.1311, found *m/e* 268.1549.

Ethyl Methyl 3-(3-Butenyl)-2-oxo-1,1-cyclohexanedicarboxylate (51). The same procedure as in **50** was used substituting 0.30 g. (12.5 mmoles) of oil-free NaH, 2.49 g. (12.0 mmoles) of **46**, 2.95 g (13.2 mmoles) of $Mg(ClO_4)_2$, and 1.31 g (12.1 mmoles) of ethyl chloroformate. After distillation, 2.43 g. (8.60 mmoles, 72%), of **51** was obtained as a colorless clear oil bp 133-135° C (0.10 mm Hg). ^1H NMR δ 5.7 (m, 1 H), 4.9 (dd, 2 H, J = 9.2, 18.9 Hz), 4.3 (m, 2 H), 3.8 (s, 3 H), 2.7 (m, 2 H), 2.4-1.3 (cplx, 9 H), 1.3 (m, 3 H); ^{13}C NMR δ 204.3, 168.0, 138.2, 114.8, 70.3, 62.1, 52.8, 48.5, 34.2, 33.9, 30.9, 28.4, 22.0, 13.9; IR (thin film), 3050, 2910, 2840, 1740, 1725, 1710, 1630, 1440, 900 cm^{-1}. HRMS, exact mass calculated for $C_{15}H_{22}O_3$, *m/e* 282.1467, found *m/e* 282.1475.

Ethyl Methyl 3-(4-Ethoxycarbonyl-3-butenyl)-2-oxocyclopentane-1,1-dicarboxylate (52). Diester **50** was ozonized using the same procedure as in ester **48**. In the round-bottomed flask 4.44 g, (16.5 mmoles) of **50** was ozonized for 1 hr in methanol. The crude aldehyde was treated with 5.74 g, (16.5 mmoles) of carboethoxy-methylene triphenylphosphorane and refluxed overnight in benzene. After work-up and chromatography 1.00 g (2.94 mmoles), 18% yield, of **52** was isolated as a clear, colorless oil. ^1H NMR δ 6.9 (dt, 1 H, J = 1.7, 6.9 Hz), 5.8 (d, 1 H, J = 15.7 Hz), 4.2 (m, 4 H),

3.8 (s, 3 H), 2.8-1.4 (cplx, 9 H), 1.3 (m, 6 H); ^{13}C NMR δ 209, 173.7, 166.7, 147.9, 122.5, 68.3, 62.7, 60.6, 53.5, 51.9, 48.4, 31.8, 31.1, 30.0, 29.0, 26.6, 14.5

Ethyl Methyl-3-(4-Ethoxycarbonyl-3-butenyl)-2-oxocyclohexane-1,1-dicarboxylate (53). The triester was ozonized and the Wittig reaction was performed as in **52**, using 3.70 g (13.1 mmoles) of **15** and 2.70 g (7.80 mmoles) of the ylide. Following chromatography 1.46 g (4.10 mmoles) of **16** was isolated as a clear colorless oil. ^1H NMR δ 6.9 (dt, 1 H, J = 1.7, 6.9 Hz), 5.8 (d, 1 H, J = 15.7 Hz), 4.3 (q, 2 H, J = 7.1 Hz), 4.2 (q, 2 H, J = 7.1 Hz), 3.8 (s, 3 H), 2.7 (m, 2 H), 2.5-1.4 (cplx, 9 H), 1.2 (m, 6 H); ^{13}C NMR δ 204.0, 167.8, 166.3, 148.2, 121.5, 70.1, 62.1, 60.0, 52.7, 48.4, 34.1, 34.0, 29.3, 27.7, 21.8, 14.1, 13.7.

Ethyl 2-(2-Ethoxycarbonylmethyl)-8-oxobicyclo[3.2.1]octanoate (54). In a 15 mL round-bottomed flask 0.63 g, (1.85 mmoles) of triester **52** was dissolved in 5 mL of HMPA. To this 0.24 g, (5.55 mmoles) of anhydrous LiCl was added and the reaction heated at 135° C for 14 h. The crude reaction mixture was quenched and worked-up following the procedure for **49**. Chromatography on a preparative TLC plate afforded 0.04 g (0.14 mmoles, 14%) of **54** as a pale yellow oil. ^1H NMR δ 4.1 (q, 4 H, J = 7.1), 2.6-1.4 (cplx, 11 H), 1.2 (t, 6 H, J = 7.1 Hz), 1.1 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 222.2, 173.5, 60.5, 51.5, 47.9, 46.7, 44.8, 42.1, 35.0, 33.0, 32.1, 27.6, 16.9, 15.1, 14.2.

Ethyl 2-(2-Ethoxycarbonylmethyl)-9-oxobicyclo[3.3.1]nonanoate (55). Triester **53** was cyclized using the procedure for **54**, 0.70 g (2.0 mmoles) of 53 and 0.25 g (5.9 mmoles) of LiCl were heated to 120°C in 5 mL of HMPA for 5 h. The crude yellow oil was chromatographed over silica gel before isolation of the products by preparative TLC. The band with the lowest R_f afforded 0.08 g (0.27 mmoles, 14%) of **55** as a pale yellow oil. ^1H NMR δ 4.2 (m, 4 H), 2.6-1.4 (m, 12 H), 1.3 (m, 6 H), 1.0 (d, 3 H, J = 11.1 Hz); ^{13}C NMR δ 219.9, 172.7, 60.5, 48.9, 46.1, 45.9, 42.7, 36.6, 36.0, 34.5, 33.7, 32.7, 27.6, 21.9, 21.4, 14.1

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Scope of Study: The synthesis of Methyl 3-(4-Ethoxycarbonyl-3-butenyl)-1-methyl-2-oxocyclohexanecarboxylate, **47**; Ethyl Methyl 3-(4-Ethoxycarbonyl-3-butenyl)-2-oxo-1,1-cyclopentanecarboxylate, **52**; and Ethyl Methyl 3-(4-Ethoxycarbonyl-3-butenyl)-2-oxo-cyclohexanecarboxylate, **53**, is described. Cyclization of these compounds was attempted using a tandem decarboxylation Michael addition sequence as an entry to the bicyclo[3.2.1]octan-8-ones and bicyclo[3.3.1]nonan-9-ones.

Findings and Conclusions: Heating **47** with 3 equivalents of LiCl in HMPA afforded only the uncyclized decarboxylation product Ethyl 5-(3-Methyl-2-oxocyclohexyl)-2-pentanoate **49** as a mixture of the cis and trans 2,6-disubstituted cyclohexanones. The stereochemistry of the decarboxylation product was found to be temperature dependent. The percentage of cis isomer was found to be 46% at 60°C and in excess of 90% at 120°C. The cyclization of **52** afforded the substituted bicyclo[3 2.1]octan-8-one **54** in 14% yield. Cyclization of **53** afforded the substituted bicyclo[3.3.1]-nonan-9-one **55** in 14% yield. Alternative synthetic routes are suggested for further investigation.

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