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THE IRON MEDIATED (1,5)-HOMOLOGOUS MICHAEL REACTION AS A ROUTE TO SPIROCYCLIC RING SYSTEMS

by

ANNE CHARLTON

A thesis submitted to the
Faculty of Graduate Studies and Research through the
Department of Chemistry and Biochemistry
in partial fulfillment of
the requirements for the Degree of Master of Science
at the University of Windsor

Windsor, Ontario, Canada

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ABSTRACT

The reaction between γ-acetoxy-α,β-unsaturated esters with diiron nonacarbonyl produces the η^2-iron tetracarbonyl complexes. Addition of a Lewis acid, such as boron trifluoride etherate, produces η^3-iron allyl cationic complexes. These complexes react with silyl enol ethers and silyl ketene acetals to afford the addition products. The regiochemistry is such that the addition occurs at the terminus of the allyl fragment remote from the ester function to produce γ substitution products. The geometric stability of the iron allyl cation allows the stereochemical integrity of the double bond to remain intact during the course of the reaction. Cyclic silyl ketene acetals and silyl enol ethers provide difunctionalized cyclic products containing a quaternary centre. These products are precursors to a variety of spirocyclic ring systems.

Three types of spirocyclizations were performed with the iron allyl addition products. Attempts at cyclizing the alkene failed to produce any product cleanly, so the compounds were first hydrogenated. The Dieckmann and the acyloin condensations produced the corresponding spirocycles. Cyclization by metal halogen exchange also formed a spirocycle in low yield.

Further investigation of this reaction and its application to natural product synthesis will be discussed.

" Sad to say I must be on my way

So buy me beer and whiskey cos I'm going far away."

- The Pogues

DEDICATION

This thesis is dedicated to my parents, for emphasizing the value of a good education.

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TABLE OF CONTENTS

ABSTRACT	iv
DEDICATION	vi
ACKNOWLEDGEMENTS	vii
LIST OF TABLES	x
LIST OF FIGURES	xi
LIST OF SCHEMES	xiv
LIST OF ABBREVIATIONS	xv
CHAPTER ONE - INTRODUCTION	1
Nucleophilic Attack on a Cyclopropane Ring.	2
Nucleophilic Attack on Bromo crotonates	6
Miscellaneous Reactions	8
π-Allyl Palladium Complexes	9
Cobalt Stabilized Propargyl Cations	15
Cuprate Additions	18
Cationic Iron Tetracarbonyl Allyl Complexes	19
Aim of Study	27
CHAPTER TWO - RESULTS AND DISCUSSION	28
FUTURE WORK	43
CONCLUSION	46
EXPERIMENTAL	47

REFERENCES 73

VITA AUCTORIS 77

LIST OF TABLES

Table 1 The results of the homologous (1,5)-Michael Reaction with substrate 32

Table 2 Results of the Dieckmann condensation 37

Table 3 The results of the acyloin condensation 38

LIST OF FIGURES

Figure 1 Polarities in an α,β-unsaturated carbonyl compound 2

Figure 2 Nucleophilic addition to an activated cyclopropane ring 2

Figure 3 The synthesis of bicyclic ring systems by intramolecular attack 3

Figure 4 Intermolecular attack on cyclopropane rings 4

Figure 5 Spirocycle formation using a cyclopropyl phosphonium salt 4

Figure 6 Lactam formation using a cyclopropyl phosphonium salt 5

Figure 7 Cuprate addition to strained cyclopropanes 6

Figure 8 Addition of trialkylboranes to bromocrotonates 7

Figure 9 Addition of a Reformatski reagent to bromocrotonates 7

Figure 10 The synthesis of enals 8

Figure 11 Addition of nucleophiles to alkynes catalyzed with Ph_3P 9

Figure 12 Addition of malonate anions to palladium allyls 10

Figure 13 Nucleophilic addition to the palladium allyl complex of mesityl oxide 11

Figure 14 Nucleophilic attack on steroids 12

Figure 15 Regio and stereoselective addition to palladium allyls 14

Figure 16 Nucleophilic addition to α,β–unsaturated nitriles 14

Figure 17 Alkyne complexation to cobalt hexacarbonyl 16

Figure 18 Nucleophilic addition to cobalt stabilized cations 16

Figure 19 Formation of *syn* isomer using cobalt propargyl cations 18

Figure 20 Addition of BuCu-$(AlCl_3)_n$ to α,β-unsaturated esters 18

Figure 21 Butylation of seven membered ring α,β-unsaturated ester 19

Figure 22 Stereospecific cation formation 21

Figure 23 Stereo and regiospecific formation of allylsilanes 22

Figure 24 The homologous (1,5)-Michael using α,β–unsaturated esters 23

Figure 25 The homologous (1,5)-Michael reaction using α,β-unsaturated ketones 23

Figure 26 Synthesis of enantiopure allyl pyrrolinone 26

Figure 27 Formation of precursors to spirocycles 27

Figure 28 Formation of ethyl (*E*)–4-acetoxy-2-butenoate 28

Figure 29 The synthesis of silyl enol ethers and silyl ketene acetals 30

Figure 30 Procedure for iron allyl tetracarbonyl addition reactions 31

Figure 31 The formation of quaternary centres 33

Figure 32 The formation of a 4:1 diastereomeric mixture 34

Figure 33 Alkylation of methyl substituted enolates 34

Figure 34 Hydrogenation of iron allyl adducts 36

Figure 35 The acyloin condensation 38

Figure 36 The acyloin condensation using a 4:1 diastereomeric mixture 39

Figure 37 The removal of trimethylsilyl groups 40

Figure 38 Acorenone 40

Figure 39 The McMurry coupling reaction 41

Figure 40 Preparation of the iodinated alkyl ester 42

Figure 41 Spirocyclization by metal-halogen exchange 42

Figure 42 Iron condensation reaction using *Z* substrates 43

LIST OF SCHEMES

Scheme 1 Michael initiated ring closure versus γ-substitution 6

Scheme 2 Formation of palladium allyl complex from palladium (II) alkene 10

Scheme 3 Nucleophilic addition to palladium allyls catalytically 13

Scheme 4 Formation of palladium allyls regioselectively 15

Scheme 5 Nucleophilic addition to cobalt propargyl cations of ketones and esters 17

Scheme 6 Formation of iron allyl tetracarbonyl cation 20

Scheme 7 The synthesis of enantiomerically pure sulphones 24

Scheme 8 The retrosynthetic pathway of the female sex phermone of the banded cucumber beetle 25

Scheme 9 Preparation of ethyl (*E*)-4-acetoxy-2-pentenoate 29

Scheme 10 The formation of *cis* dienolates 35

Scheme 11 Proposed synthesis of acorenone 44

LIST OF ABBREVIATIONS

Ac	acetyl
BF_3-OEt_2	boron trifluoride etherate
Bn	benzyl
Bu	butyl
n-BuLi	*normal*-butyl lithium
°C	degrees Celsius
cat	catalytic
CH_2Cl_2	methylene chloride
cm^{-1}	wavenumbers
δ	chemical shift, delta scale
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtOH	ethanol
Et_2O	diethyl ether
eq	equivalents (molar)
g	grams
h	hours
HMPA	hexamethylphosphoramide
i-Pr	isopropyl
IR	infrared

LDA	lithium diisopropylamide
m	multiplet (NMR)
M	molarity
Me	methyl
Me_3NO	trimethylamine *N*-oxide
Mhz	megahertz
mL	millilitres
mmol	millimole
MS	mass spectrometry
mp	melting point
NH_4Cl	ammonium chloride
Nu	nucleophile
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet (NMR)
s	singlet (NMR)
t	triplet (NMR)
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
tlc	thin layer chromatography

TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl iodide

Chapter One

INTRODUCTION

The reversal of polarities which are conferred upon a molecule by the functional groups it contains is termed umpolung reactivity.[1] This type of transformation has generated much interest due to its ability to provide new synthetic pathways. For example, normally the electronegativity of the oxygen atom polarizes a carbonyl function to allow the carbon atom to carry a slightly positive charge. The reversal of this polarity provides acyl (-CR=O) and formyl (-CH=O) anions. The use of these anions in synthesis is limited due to their high reactivity, but transformations which utilize the equivalent of an acyl or formyl anion can be performed using a "masked" anion.[1]

The γ-position of an α,β-unsaturated carbonyl compound is generally considered to be negatively polarized (Figure 1). For example, dienolates derived from α,β-unsaturated carbonyl compounds are able to undergo alkylation in the γ-position.[2] The umpoled molecule would then be positively polarized in this position, and thus could be functionalized by nucleophiles. Nucleophilic addition to the γ-position of an α,β-unsaturated carbonyl compound is termed the homologous (1,5)-Michael reaction.[3]

There are few reactions by which this type of transformation can be achieved. Ordinarily, it is accomplished using functionalized cyclopropane rings.[3] In this case, the carbon backbone of the electrophile rearranges. Organometallic complexes, such as allyl palladiums, cobalt propargyl cations and iron allyl cations have been successfully employed as γ cation equivalents. Iron allyl cations offer a method by which to achieve

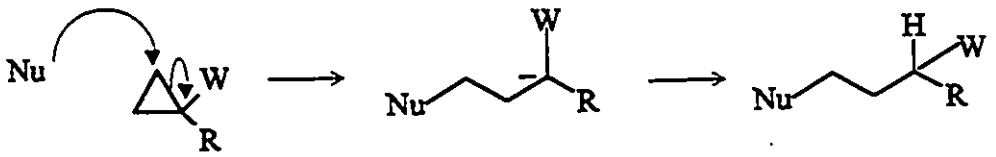
the homologous (1,5)-Michael reaction stereo and regioselectively. The compounds which successfully act as γ–cation equivalents will be presented with their applications.

Figure 1. Polarities in an α,β-unsaturated carbonyl compound

Nucleophilic Attack on a Cyclopropane Ring

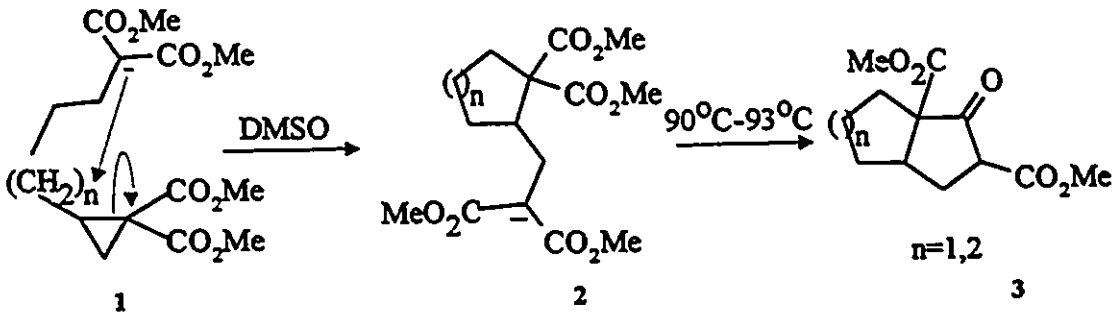
Nucleophilic attack on a cyclopropane ring is possible when the ring contains an electron withdrawing group.[3] This can be achieved with a variety of nucleophiles and the product is the equivalent of an homologous (1,5)-Michael reaction (Figure 2). The reaction can be done with a variety of nucleophiles both inter and intramolecularly.[3,4]

Figure 2. Nucleophilic addition to an activated cyclopropane ring



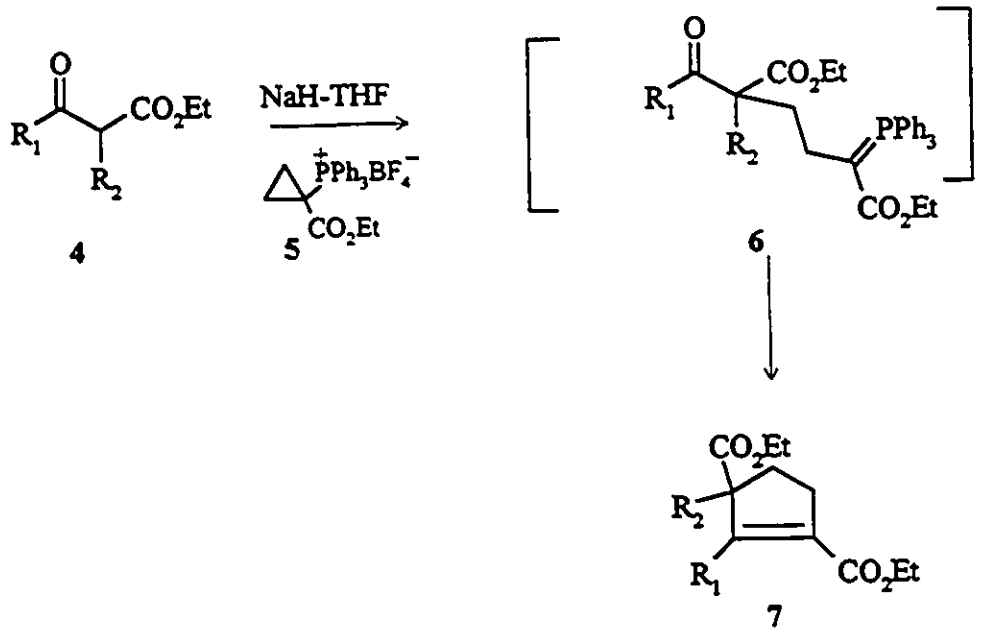
Nucleophilic attack on a cyclopropane ring followed by intramolecular ring closure is an excellent method for the synthesis of bicyclic ring systems.[3a] This is illustrated by the following sequence (Figure 3).

Figure 3. The synthesis of bicyclic ring systems by intramolecular attack



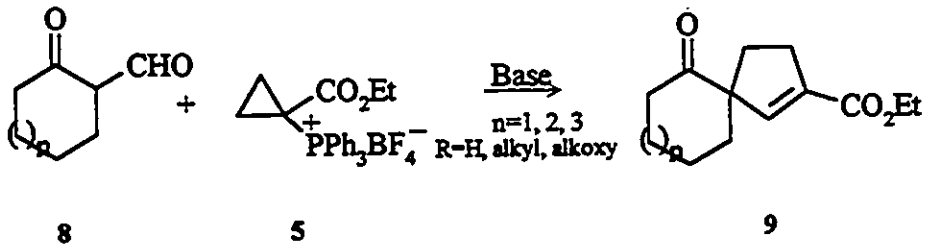
Intermolecular nucleophilic addition reactions to cyclopropane rings have also been accomplished; however, more than one activating group is required on the ring, as opposed to the intermolecular case.[3b] The reaction works well with diactivated nucleophiles such as β-keto esters or α-carboxyphosphonium salts. In the illustrated case, the phosphonium salt is converted to a phosphorane intermediate by the nucleophilic attack, and subsequently rearranges to form the indicated diester in high yield (Figure 4).[3c]

Figure 4. Intermolecular attack on cyclopropane rings



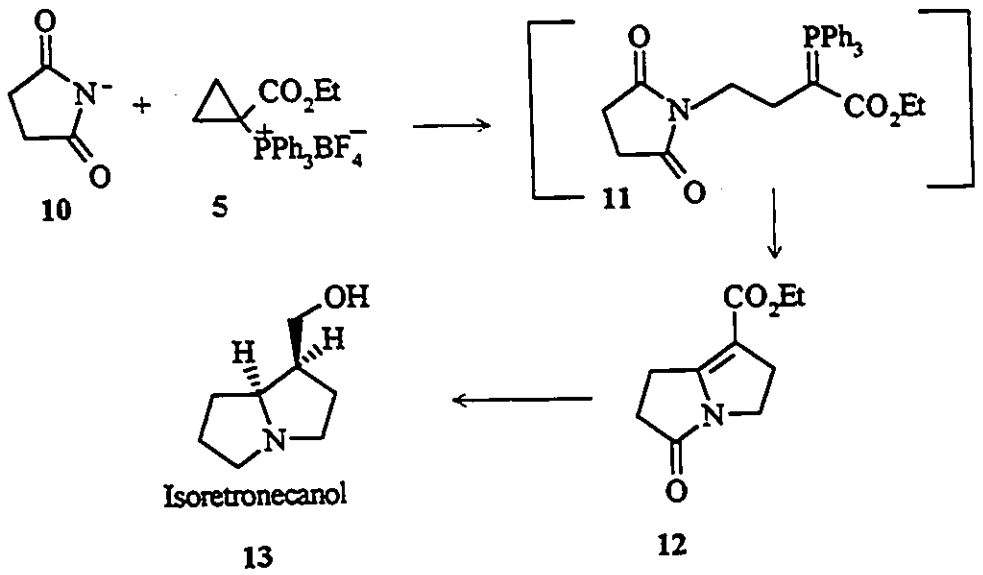
The phosphonium salt 5 has been successfully employed as a cycloalkenylation reagent. Amines and alkoxides as well as enolates can be used as the nucleophile.[3c] Spirocycles can be synthesized by reacting β-keto esters or 1,3-dicarbonyl compounds with the phosphonium salt 5 (Figure 5).[3d]

Figure 5. Spirocycle formation using a cyclopropyl phosphonium salt



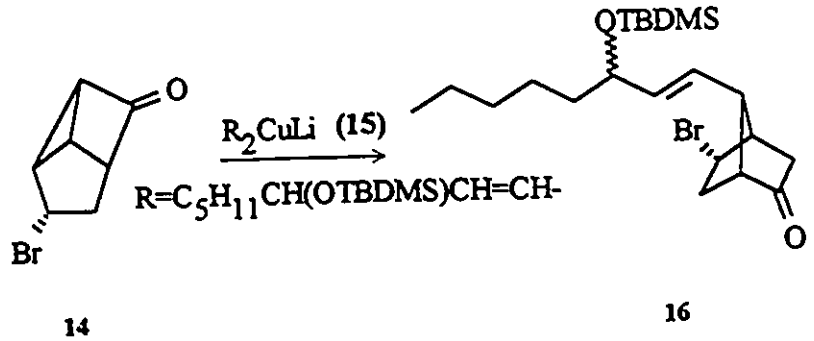
The synthetic utility of this reagent is illustrated by its reaction with succinimide anion (**10**).[3c] The bicyclic lactam is produced in high yield from the intermediate formed by nucleophilic attack on the cyclopropane ring. This lactam (**12**) is an intermediate in a synthesis of isoretronecanol (**13**) (Figure 6).[3f]

Figure 6. Lactam formation using a cyclopropyl phosphonium salt



Organocopper reagents can also be employed as nucleophiles in cyclopropane ring opening reactions. For example, cuprate reagent **15** reacts with the tricyclic ketone **14** to produce the norbornanone **16**, which is a precursor to certain prostaglandins.[3g] The cuprate reagent attacks on the least hindered side of the substrate; this dictates the stereochemistry of the product (Figure 7).[3]

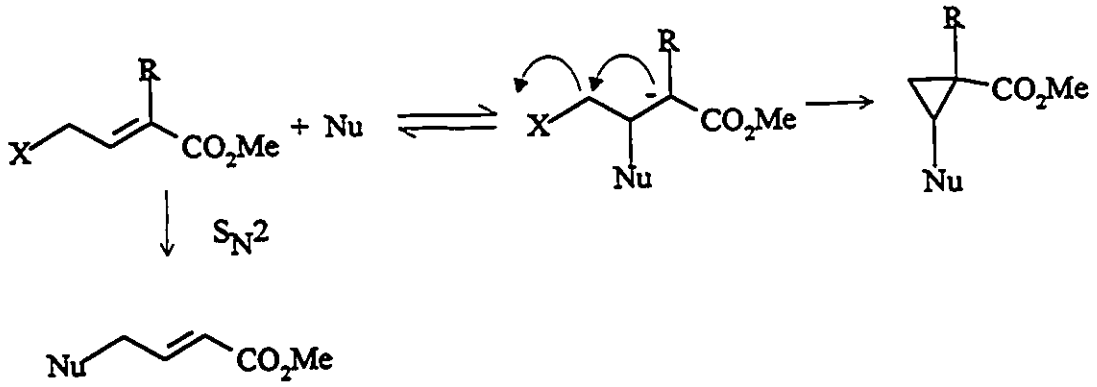
Figure 7. Cuprate addition to strained cyclopropanes



Nucleophilic Attack on Bromocrotonates

γ–Bromocrotonates can undergo nucleophilic substitution to provide γ-substitution products. The competing reaction is conjugate addition and subsequent intramolecular ring closure, termed the Michael initiated ring closure (MIRC) reaction. (Scheme 1).[5]

Scheme 1. Michael initiated ring closure versus γ-substitution

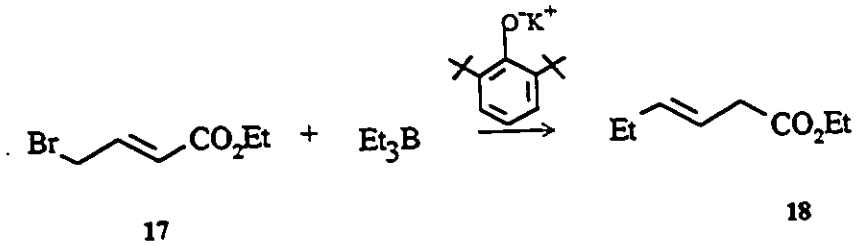


In order to obtain the product from direct displacement, highly stabilized anions must be employed as nucleophiles (i.e., malonate anion). The product obtained from

MIRC becomes predominant in cases where the nucleophile is more reactive. In order to predominantly obtain the nucleophilic displacement product, the reaction must be done in the presence of a good metal solvating agent such as HMPA.[5]

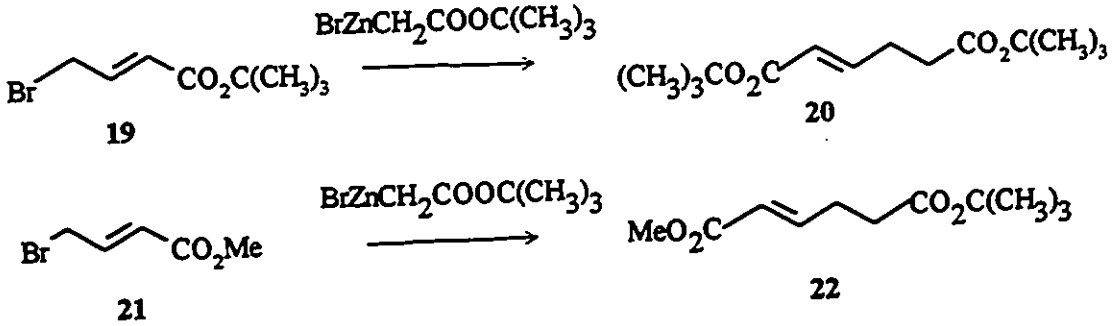
Trialkylboranes have been found to react with ethyl-4-bromocrotonate to yield unsaturated esters in the presence of 2,6-di-*t*-butylphenoxide. This, however, takes place with migration of the double bond, to produce ethyl 3-alkenoates (Figure 8).[6] This method, is of course, limited by the availability of the trialkylboranes.

Figure 8. Addition of trialkylboranes to bromo crotonates



The Reformatsky reagent, $BrZnCH_2COOC(CH_3)_3$ also reacts with bromocrotonates (**19, 21**) to yield the products of nucleophilic substitution in the γ–position in moderate yields (Figure 9).[7] In both cases, the stereochemistry of the double bond is retained.

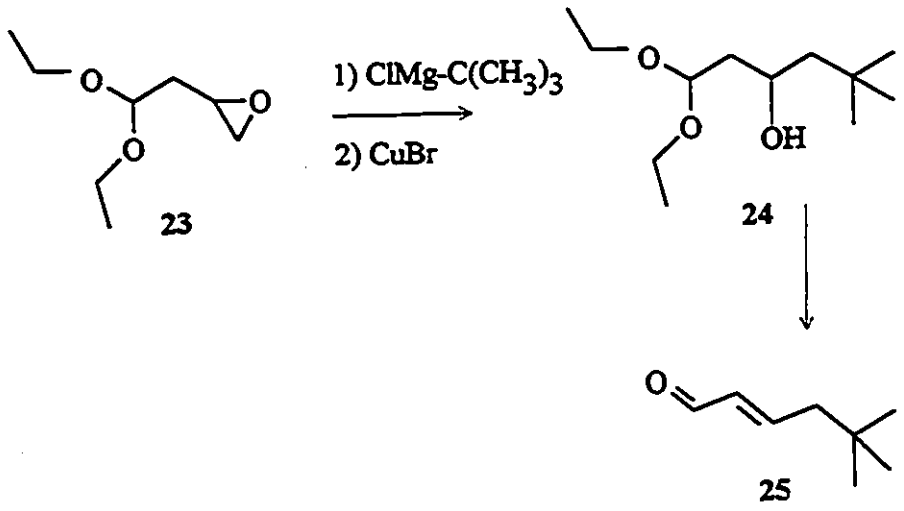
Figure 9. Addition of a Reformatski reagent to bromocrotonates



Miscellaneous Reactions

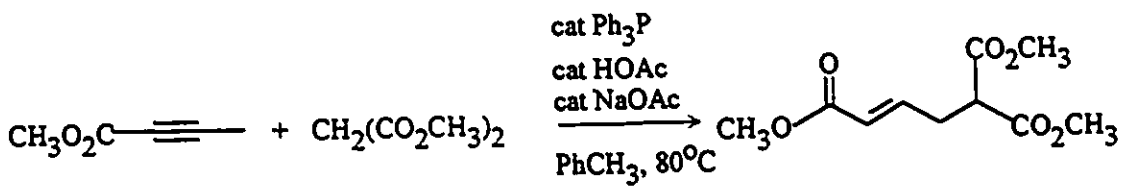
A limited number of methods have been reported which give the overall substitution products of the homo-(1,5)-Michael reaction, but without ever involving γ-functionalized alkenones or alkenoates. These have generally been limited to very specific cases, and their generality has not been investigated. For instance, the addition of organomagnesium halides to (2,2-diethoxyethyl)oxirane in the presence of a catalytic amount of CuBr affords α,β-unsaturated aldehydes [8] Hydrolysis of **24** provided an aldol which underwent immediate dehydration to afford **25**. (Figure 10). Unsaturated or functionalized Grignard reagents were also found to be successful in reaction with this oxirane.

Figure 10. The synthesis of enals



Trost has accomplished nucleophilic additions to alkynes bearing an electron withdrawing group.[9] These compounds undergo nucleophilic additions to provide *E* alkenes in the presence of a catalytic amount of triphenylphosphine. In general, nucleophiles for which the pKa is less than 16 are successful. The reaction works best with an ester or amide function on the alkyne (Figure 11).

Figure 11. Addition of nucleophiles to alkynes catalyzed with Ph_3P

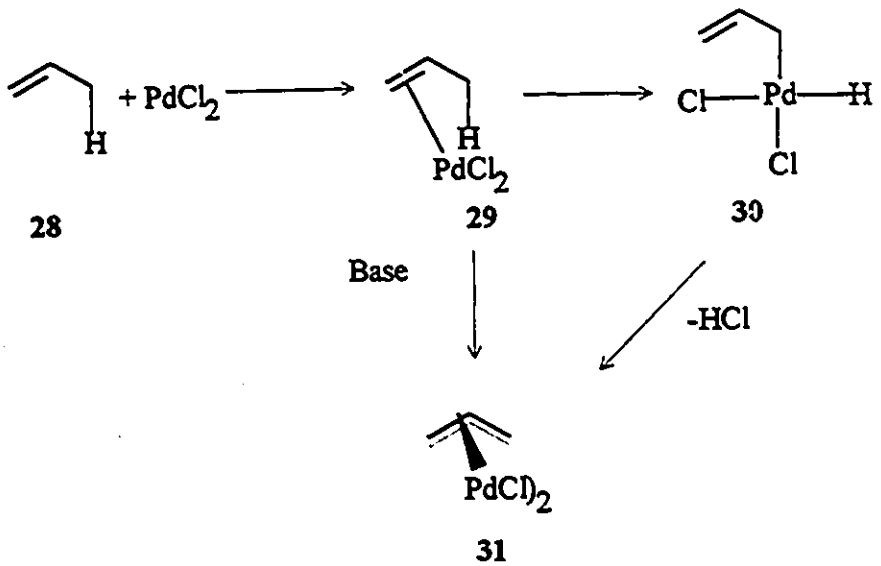


26 **27**

π–Allyl Palladium Complexes

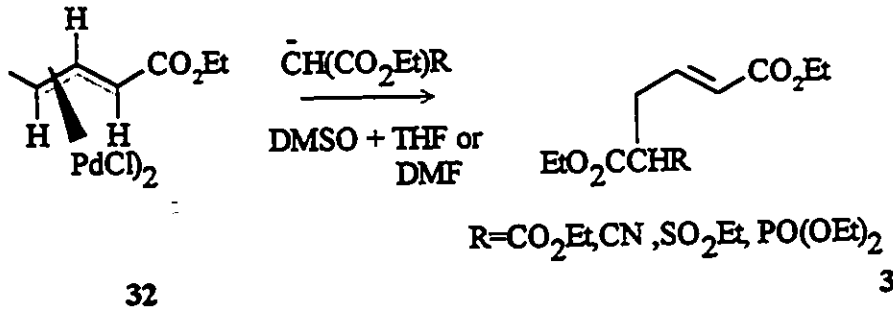
π–Allyl palladium complexes provide a means by which to functionalize in the γ–position of α,β-unsaturated carbonyl compounds. The allyl palladium complexes may be produced from the palladium (II) alkene complex by proton abstraction, or by palladium insertion into an allylic carbon-hydrogen bond (Scheme 2).[10]

Scheme 2. Formation of palladium allyl complex from palladium (II) alkene



The allyl palladium complexes derived from α,β-unsaturated ketones and esters undergo nucleophilic attack and subsequent metal displacement to produce the γ–substitution product. The di-μ-chloro-bis-[1,2,3-η^3-(1-ethoxycarbonylallyl) palladium (II)] complex reacts with malonate type anions[11] and the pyrrolidine enamine of cyclohexanone[12] to produce the γ–substitution product. The *syn* stereochemistry of the allyl palladium complex is retained to produce the *E* isomer (Figure 12).

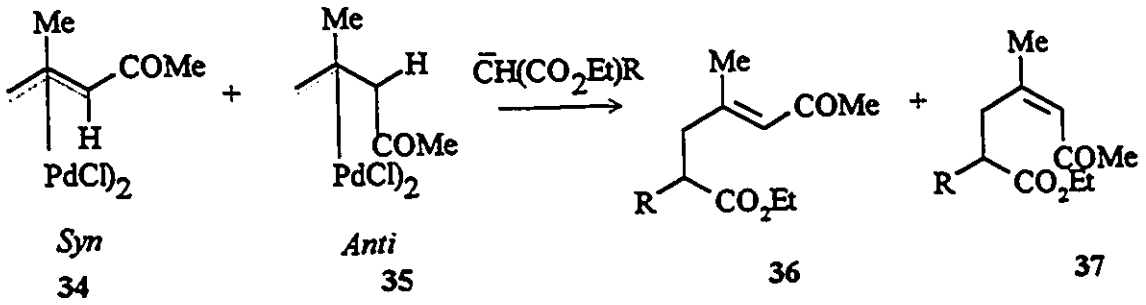
Figure 12. Addition of malonate anions to palladium allyls



As proposed by Trost and co-workers[13], an additional ligand in the reaction mixture aids substitution in the allyl system. In the absence of DMSO, no reaction occurred.

Complexation of mesityl oxide with palladium (II) chloride produced a mixture of *syn* and *anti* complexes, which reacted with malonate anions regiospecifically at the terminus of the allyl fragment remote from the carbonyl function, to yield both (*E*) and (*Z*) products (Figure 13). Generally, the (*E*) isomer was produced in excess.[11]

Figure 13. Nucleophilic addition to the palladium allyl complex of mesityl oxide

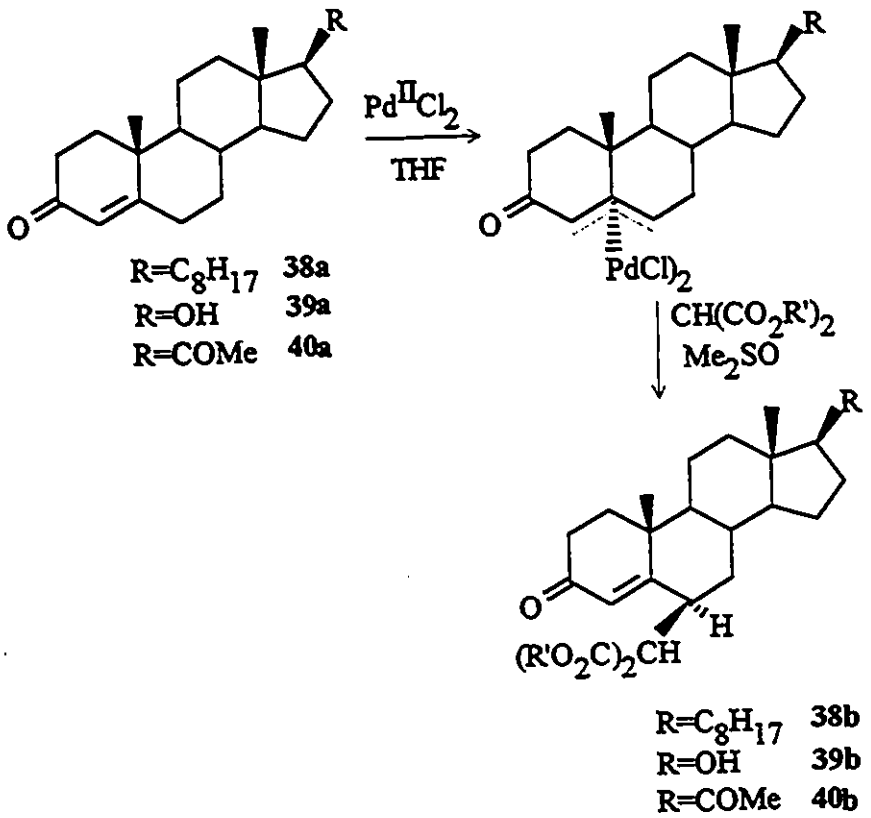


Although this is a useful transformation for carbon-carbon bond formation, the nucleophiles which are successful are restricted to those which are considered to be "soft". For example, reaction of the complexes with cyanide ion failed to produce any addition product.

This type of reaction has been applied to the synthesis of steroidal 6α and 6β malonates and acetates.[14] Cholest-4-en-3-one, testosterone and progesterone (**38a**, **39a**, **40a**) produce single diastereomers upon complexation to palladium. The palladium

coordinates to the less sterically hindered face of the alkene (Figure 14). Reaction of these complexes with malonate ion produced **38b**, **39b** and **40b** in high yields. In these cases, nucleophilic attack must occur at the face of the allyl unit opposite the palladium moiety.

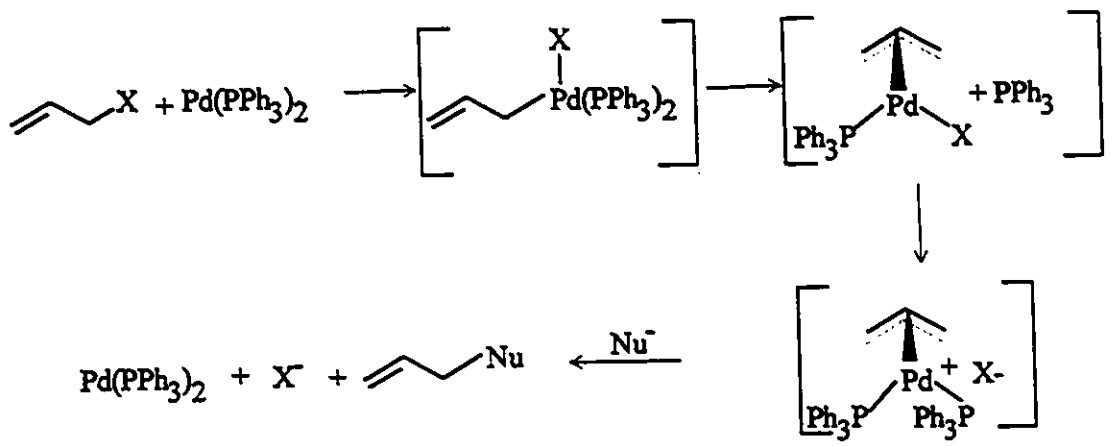
Figure 14. Nucleophilic attack on steroids



Palladium allyl complexes can be also be generated *in situ*. In this case, only a catalytic amount of palladium is required. Phosphines are generally added to increase the electron density surrounding the metal, thus aiding the oxidative addition, and also to maintain the complex in a soluble form. Additionally, the allyl palladium complex must be

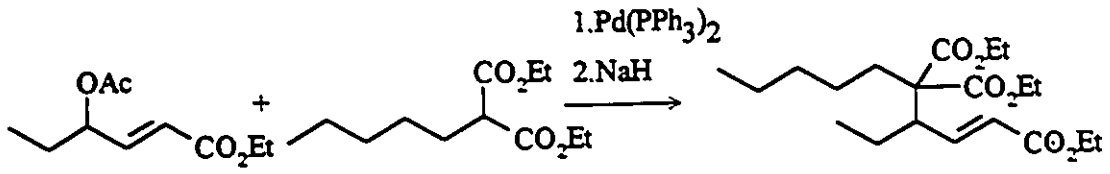
converted to a cationic form to undergo nucleophilic addition. This can be done though the addition of silver tetrafluoroborate to induce halide precipitation, or by adding a good ligand for palladium. When palladium is used catalytically, complex formation and activation, followed by nucleophilic addition, and subsequent metal displacement can be done in one reaction (Scheme 3).[10]

Scheme 3. Nucleophilic addition to palladium allyls catalytically



For instance, dimethyl pentylmalonate added to methyl 4-acetoxy-2-hexenoate exclusively at the γ position in the presence of a catalytic amount of palladium (Figure 15).[15] In this case, the stereochemical integrity of the double bond remained intact during the reaction, as the product obtained was the (*E*) isomer. The electron withdrawing nature of the carbonyl system is thought to play an important role in directing the nucleophile to the opposite end of the π-allyl fragment.

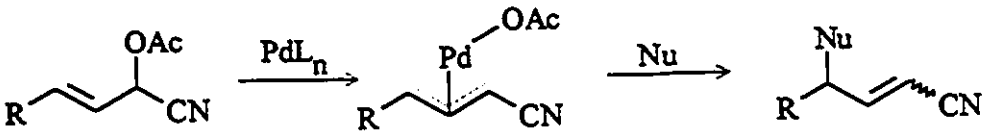
Figure 15. Regio- and stereoselective addition to palladium allyls



41 **42** **43**

α–Acetoxy–β,γ-unsaturated nitriles also undergo nucleophilic addition at the γ-position using palladium phosphine complexes catalytically (Figure 16).[15] The nucleophiles which were investigated were malonates and acetoacetates. Although the reaction is regioselective, it provides a mixture of *E* and *Z* isomers in high yield. Additional ligands on the allyl fragment were shown to decrease the yields.

Figure 16. Nucleophilic addition to α,β–unsaturated nitriles



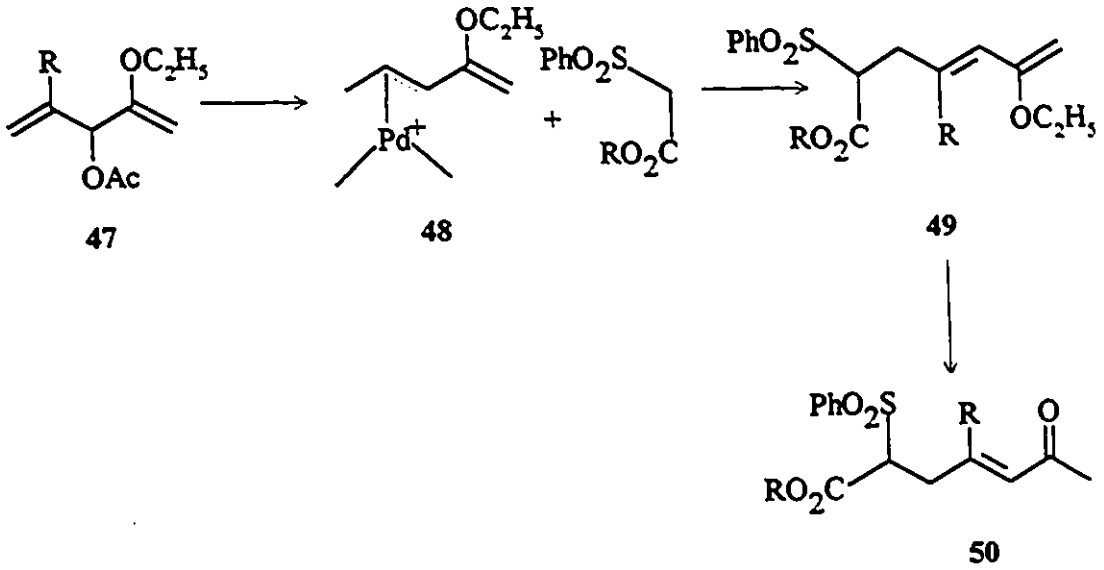
Nu=dimethyl malonate
methyl acetoacetate

44 **45** **46**

Palladium allyl complexes have been formed chemoselectively from dienes.[16] It has been shown that electron withdrawing groups assist in the formation of the complex

and that electron donating groups impede it. This allows compounds such as **47** to selectively form the palladium π-allyl complex at one end of the molecule and thus allows it to act as a vinylogous enolium ion equivalent (Scheme 4). Addition of the nucleophile shown produced **49** which was hydrolyzed to produce **50** as the *E* isomer.

Scheme 4. Formation of palladium allyls regioselectively



Cobalt Stabilized Propargyl Cations

A cobalt hexacarbonyl fragment complexes to alkynes to produce the complex **52** (Figure 17).[10] These complexes form stable propargyl cations in the presence of an acid if they contain a leaving group in the propargyl position. These cations undergo nucleophilic attack by a wide variety of nucleophiles such as electron rich arenes, β-dicarbonyls, ketones and enol derivatives, allylsilanes and hydrides (Figure 18).[17] This reaction was

developed by Nicholas and provides a synthetic means for propargylation without the common problem of allene formation.[17]

Figure 17. Alkyne complexation to cobalt hexacarbonyl

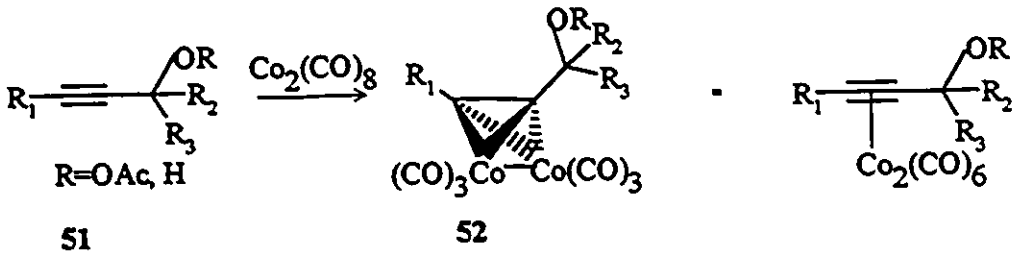
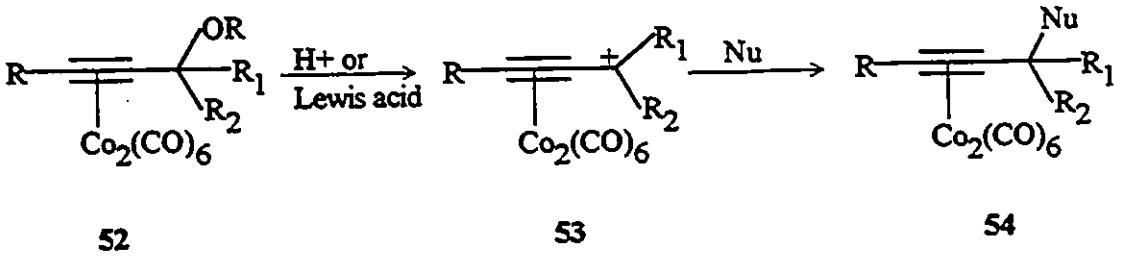


Figure 18. Nucleophilic addition to cobalt stabilized cations

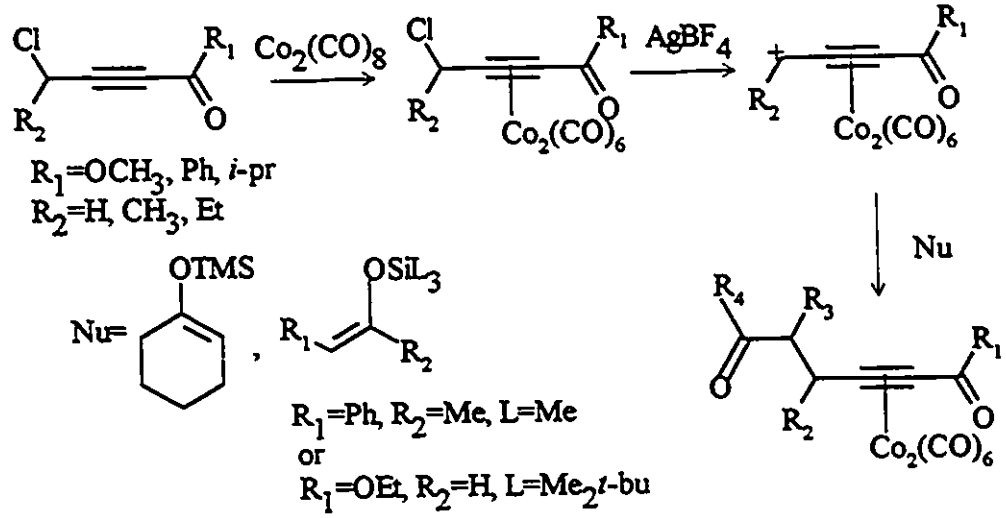


In the case of ketones, attack generally occurs at the more substituted α carbon. Demetallation of the resultant product can be achieved by the addition of an oxidant such as ceric ammonium nitrate.[18]

The reaction has been developed further to include alkynones and alkynoates.[18] This would allow the complexes to act as γ-carbonyl cation equivalents. The γ–chloro carbonyl substrates were chosen for this study due to the lack of reactivity of the γ-

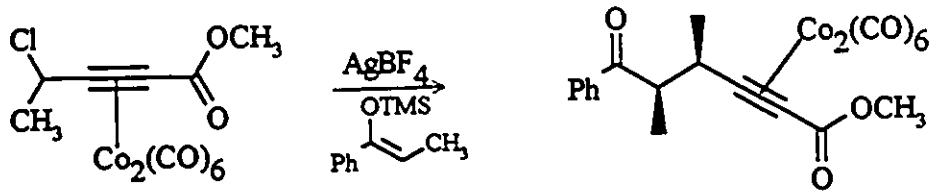
hydroxy and γ-alkoxy compounds with either Brønstead or Lewis acids. This was attributed in part, to the presence of two Lewis basic sites. Complexation to cobalt hexacarbonyl, followed by addition of silver tetrafluoroborate and subsequent addition of a nucleophile, produced the coupling products. The reaction presumably occurs through a cobalt propargyl cationic intermediate. The nucleophiles employed were silyl enol ethers, the silyl ketene acetal of ethyl acetate and allyltins (Scheme 5).[18]

Scheme 5. Nucleophilic addition to cobalt propargyl cations of ketones and esters



When substrates containing γ-alkyl substituents were reacted with the silyl enol ether of propiophenone, a mixture of diastereomers was produced with one present in excess. Crystallographic analysis of one of these products indicated the major isomer to be *syn* (Figure 19).[18]

Figure 19. Formation of *syn* isomer using cobalt propargyl cations



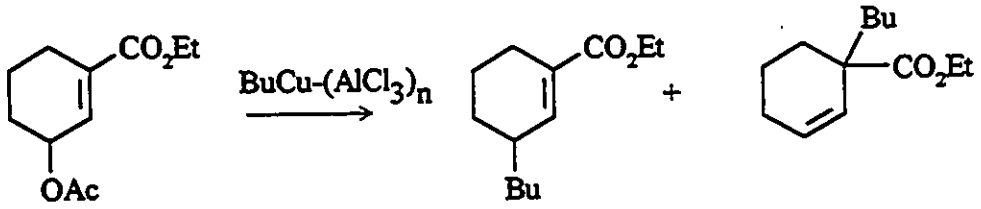
55 56

8.7:1 syn: anti

Cuprate Additions

Cyclic γ-acetoxy-α,β-unsaturated esters react with BuCu-$(AlCl_3)_n$ to produce a mixture of α- and γ- butylated esters in high yield.[19] High regioselectivity for the γ-position (97:3) can be achieved by preparing the copper reagent with at least two moles of $AlCl_3$ per mole of BuCu (Figure 20).

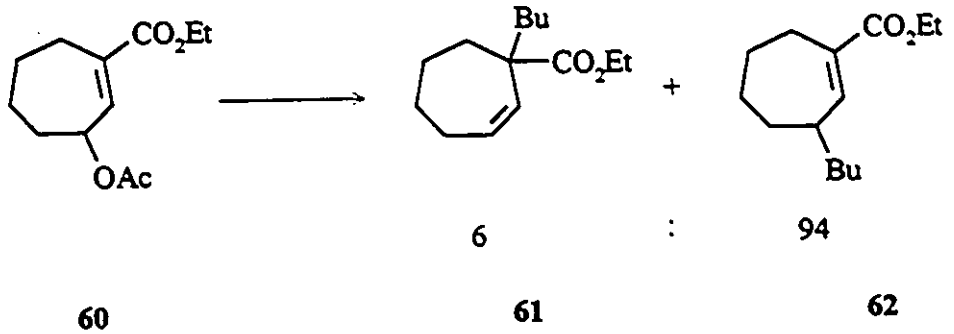
Figure 20. Addition of BuCu-$(AlCl_3)_n$ to α,β-unsaturated esters



57 58 59

The α,β-unsaturated ester of the seven membered ring shown below was also butylated in the γ-position regioselectively and in good yield (Figure 21).[19]

Figure 21. Butylation of seven membered α,β-unsaturated ester



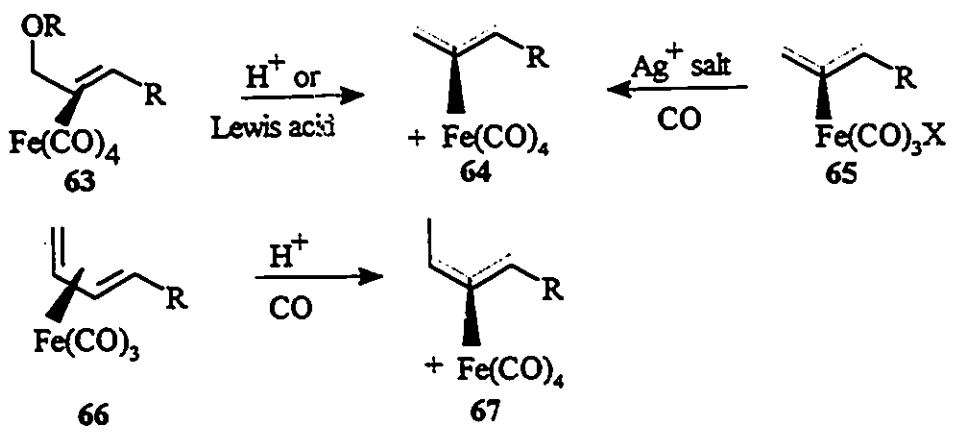
Although the reactions presented thus far can provide a means by which to obtain a γ-carbonyl cation equivalent, most are highly limited. Nucleophilic attack on cyclopropyl rings can provide the homologous (1,5)-Michael reaction product; however, this transformation requires the breaking of the carbon backbone of the electrophile. The version of this reaction in which the carbon backbone remains intact would be beneficial. Allylpalladium complexes allow this type of transformation however, the type of nucleophiles which can be employed are usually limited to highly stabilized malonates. In addition, the stereochemistry of the product is often unpredictable, with the (*E*) isomer often present in excess. The use of palladium allyls, along with other methods discussed, frequently suffer from poor regioselectivity.

Cationic Iron Tetracarbonyl Allyl Complexes

Iron allyl cations provide an excellent method by which to functionalize an alkene both regio- and stereospecifically. There are three main methods of producing these allyl

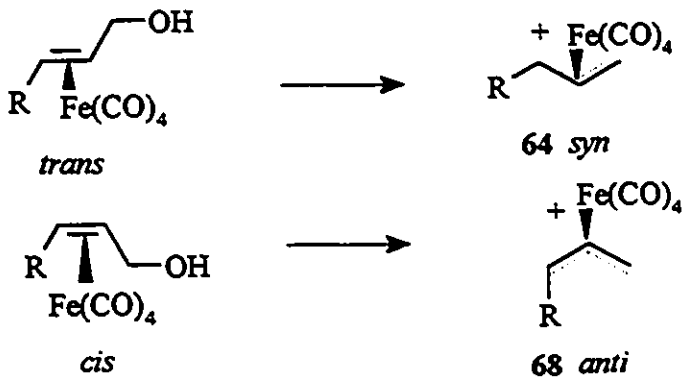
cations (Scheme 6).[20] The first involves initial complexation of an iron tetracarbonyl unit to an alkene and subsequent ionization of the ether, alcohol or acetate function using a strong protic acid or a Lewis acid. The second method involves the initial reaction of allyl halides with iron pentacarbonyl or diiron nonacarbonyl, which results in oxidative addition of the C-X bond to form (η^3-allyl)$Fe(CO)_3X$ complexes (**65**). Addition of silver salts in the presence of carbon monoxide produces the iron allyl cationic complexes. The third method involves complexation of dienes to form η^4-iron tricarbonyl complexes (**66**), followed by the addition of a strong protic acid in the presence of carbon monoxide. The acid protonates the diene and allows the iron atom to coordinate to another carbon monoxide ligand, forming the iron allyl cation. In this case, the carbon atom protonated ends up as a *anti* substituent (**67**).

Scheme 6. Formation of iron allyl tetracarbonyl cation



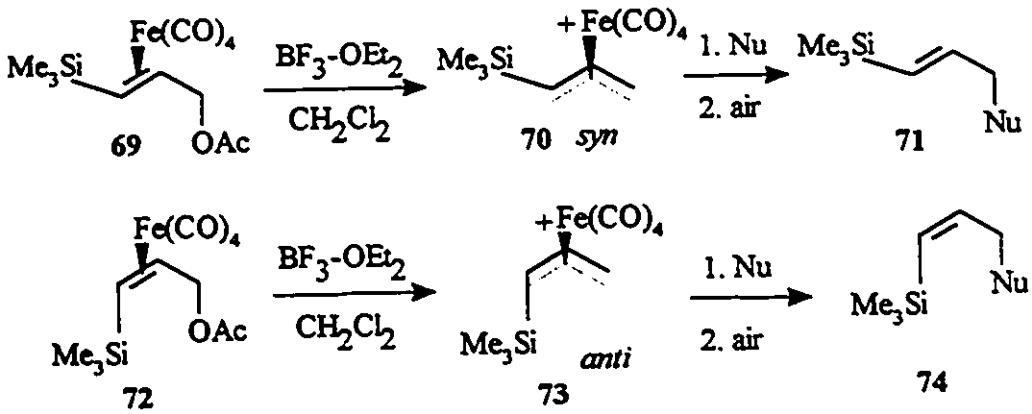
Formation of the cation is stereospecific (Figure 22). Once formed, these cations are geometrically stable and will not interconvert unless heated.[21] This allows reactions to proceed with the stereochemical integrity of the double bond intact. These complexes undergo nucleophilic additions generally on the least substituted terminus of the allyl fragment by phosphines[22], amines[22], highly stabilized carbanions[22], electron rich arenes[23], dialkylcadmiums[24], Grignard reagents[25], zinc cyanocuprates[26], allylsilanes[27], allyl stannanes, silyl enol ethers and silyl ketene acetals.[28]

Figure 22. Stereospecific cation formation



Vinylsilanes have been synthesized using iron allyl cations stereospecifically in moderate to good yields (Figure 23).[28a] In the case of the *syn* isomer, (70), the stereochemistry was completely retained. Nucleophilic addition to the *anti* isomer (73) formed products with almost total retention of stereochemistry (*Z*:*E*=96:4). In all cases, the addition was exclusively γ– to the trimethylsilyl group. The nucleophiles employed were silyl enol ethers, silylketene acetals, and allyltins.

Figure 23. Stereo and regiospecific formation of allylsilanes

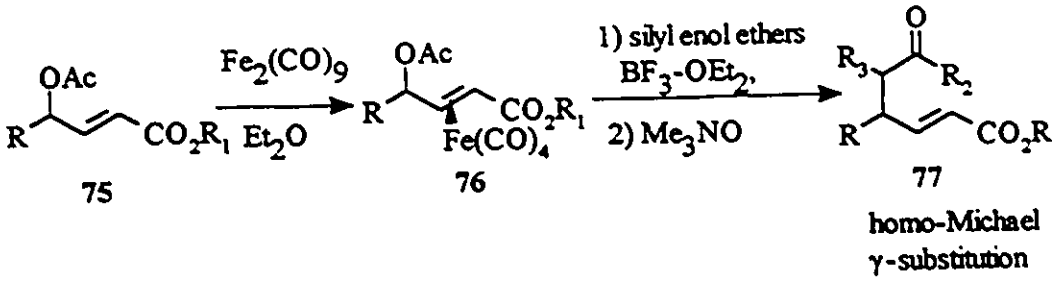


Nu = silyl enol ethers, o-silyl vinyl ketene acetal, allyltin

43-71%

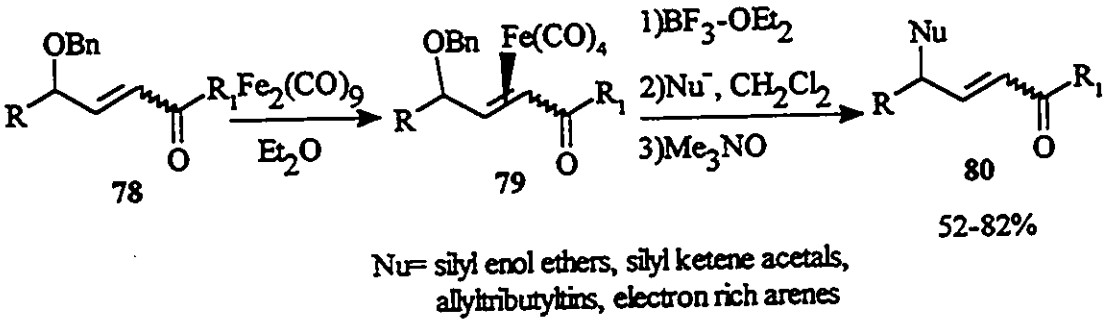
The effect of a polar group on the nucleophilic addition was investigated by employing α,β-unsaturated ketones[28b] and esters.[28c] The iron tetracarbonyl complexes of γ-acetoxy-α,β-unsaturated esters were shown to undergo nucleophilic addition in the presence of a Lewis acid through the intermediacy of an iron allyl cationic complex to provide the γ-substitution product. The nucleophile was found to attack regiospecifically at the terminus remote from the ester function even where the γ- R was large, such as phenyl, (76-77), thereby providing a route to 1,6-dicarbonyl compounds. This strongly suggests that the polar nature of the ester function is capable of overriding any steric effect. The reaction was also stereospecific, allowing retention of configuration about the double bond (Figure 24).

Figure 24. The homologous (1,5)- Michael using α,β–unsaturated esters



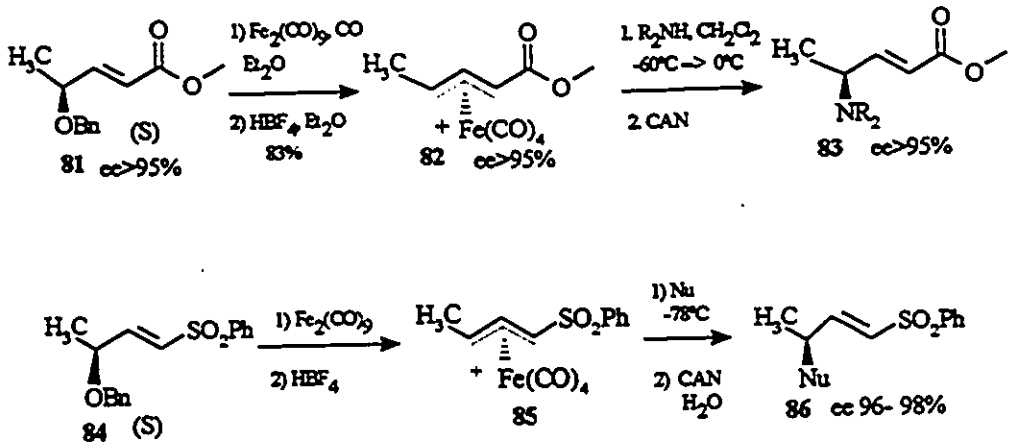
The iron tetracarbonyl complexes of γ-benzyloxy-α,β-unsaturated ketones provided similar results.[28b] When the starting alkene was of the *E* configuration, total stereochemical retention was realized, and using the *Z* isomer, ratios of approximately 97:3 *Z*:*E* were isolated. The reaction was also regioselective with attack occurring at the terminus of the allyl fragment opposite the carbonyl group (Figure 25).

Figure 25. The homologous (1,5)-Michael reaction using α,β-unsaturated ketones



Enders and co-workers have synthesized 4-aminoenoates[29] and alkenyl sulphones[30] of high enantiomeric purity using iron allyl cationic complexes. Complexation of one enantiomer of the α,β-unsaturated compound (**81**) to an iron tetracarbonyl fragment and subsequent addition of tetrafluoroboric acid provides an iron allyl cationic complex (**82**) which exhibits planar chirality. These complexes undergo attack by various nucleophiles to yield products of high enantiomeric purity after decomplexation. Nucleophilic attack occurs at the face of the alkene opposite the bulky iron tetracarbonyl group for both the ester and sulphone compounds. In all cases, the product formed is that of γ-attack (Scheme 7). A variety of carbon and nitrogen based nucleophiles were added to the sulphones but, only amines were employed in the case of the α,β–unsaturated esters.

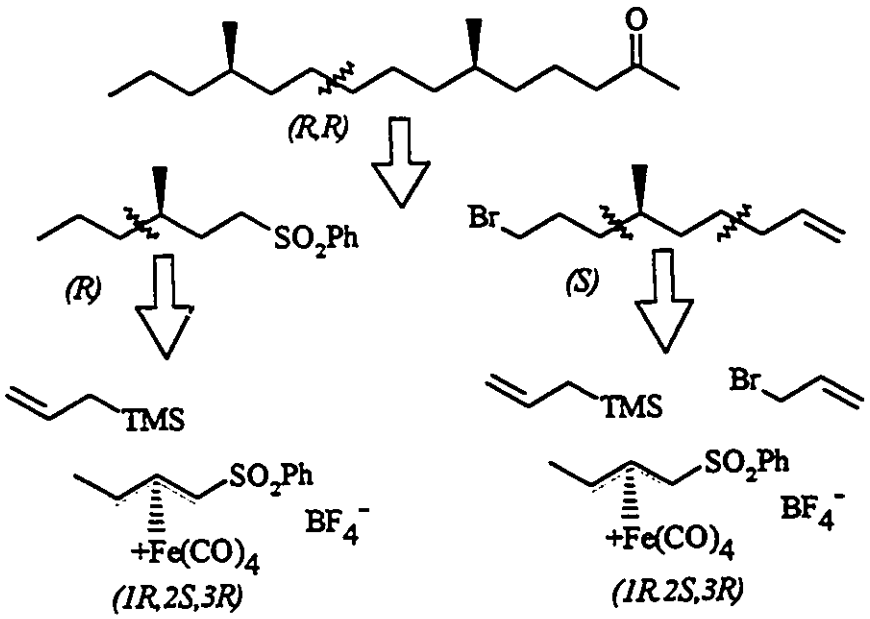
Scheme 7. The synthesis of enantiomerically pure sulphones



Nu = $LiCH(CO_2Me)_2$, 1,3,5-$(MeO)_3C_6H_3$, silyl enol ethers, silyl ketene acetals.

This type of reaction was applied to a synthesis of dimethylpentadecan-2-one, which is the female sex pheromone of the banded cucumber beetle.[31] The retrosynthetic pathway is shown below (Scheme 8).

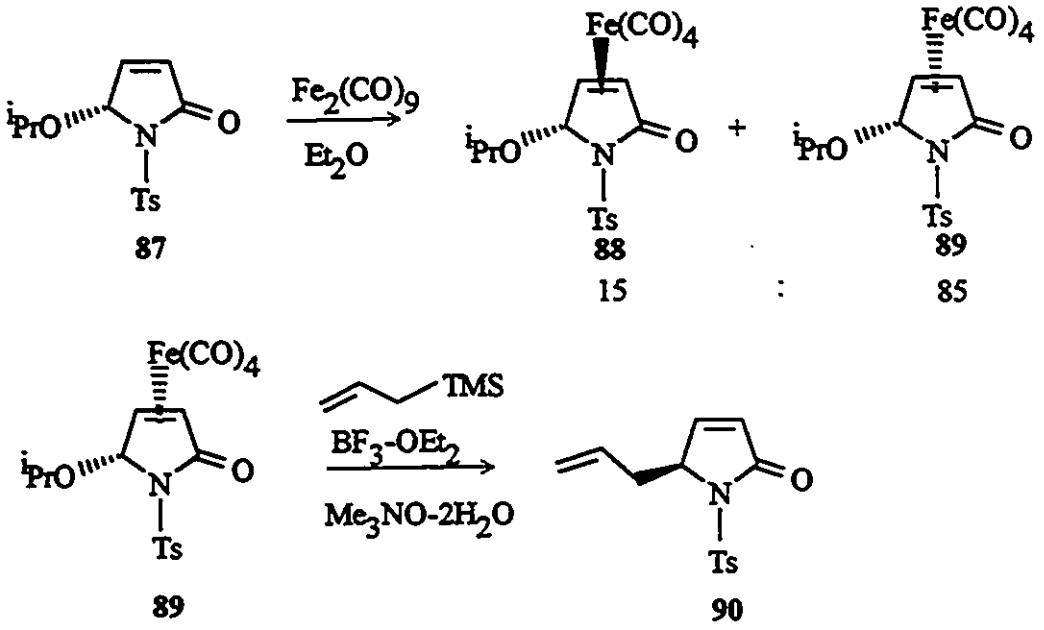
Scheme 8. The retrosynthetic pathway of the female sex pheromone of the banded cucumber beetle



The target molecule can be disconnected into the two compounds shown. The first of these can be synthesized using allylsilane and the iron allyl cation shown. The second of these can be produced in nine steps using allylsilane, allyl bromide and the same iron allyl cation. The sex pheromone of the female banded cucumber beetle was synthesized in high enantiomeric and diastereomeric purity in 39% overall yield for thirteen steps.[31]

Enantiopure 5-substituted pyrrolinones have been synthesized through iron tetracarbonyl mediation.[32] Pyrrolinone **87** was complexed to iron tetracarbonyl producing a ratio of diastereomers (85:15 *cis*:*trans*). The preference for the *cis* isomer was attributed to the precoordination of the of the iron tetracarbonyl group to the oxygen of the isopropoxy group. The *cis* isomer was easily purified and reacted with allyltrimethylsilane in the presence of BF_3-OEt_2 to yield the *trans*-5-allyl complex which, after decomplexation, produced the enantiopure 5-allyl pyrrolinone (**90**) in 88% yield (Figure 26).

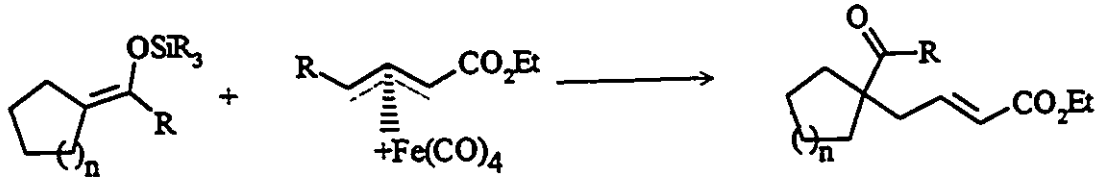
Figure 26. Synthesis of enantiopure allyl pyrrolinone



Aim Of Study

The focus of this thesis is to employ the homologous (1,5)- Michael reaction of α,β-unsaturated esters to produce precursors to spirocyclic ring systems. In order to achieve this, functionalized cyclic nucleophiles must be added to the carboxy substituted tetracarbonyliron allyl cation (Figure 27). This would result in the formation of a quaternary centre. This method could potentially provide a route to a variety of spirocycles by varying the ring size of the nucleophile and the method of spirocyclization. There are many methods by which to close the iron allyl adducts which would form different sized rings.

Figure 27. Formation of precursors to spirocycles

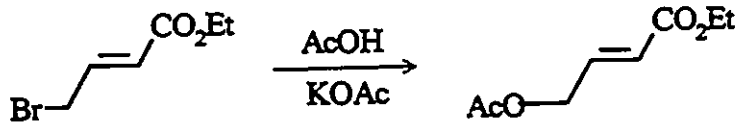


Chapter Two

RESULTS AND DISCUSSION

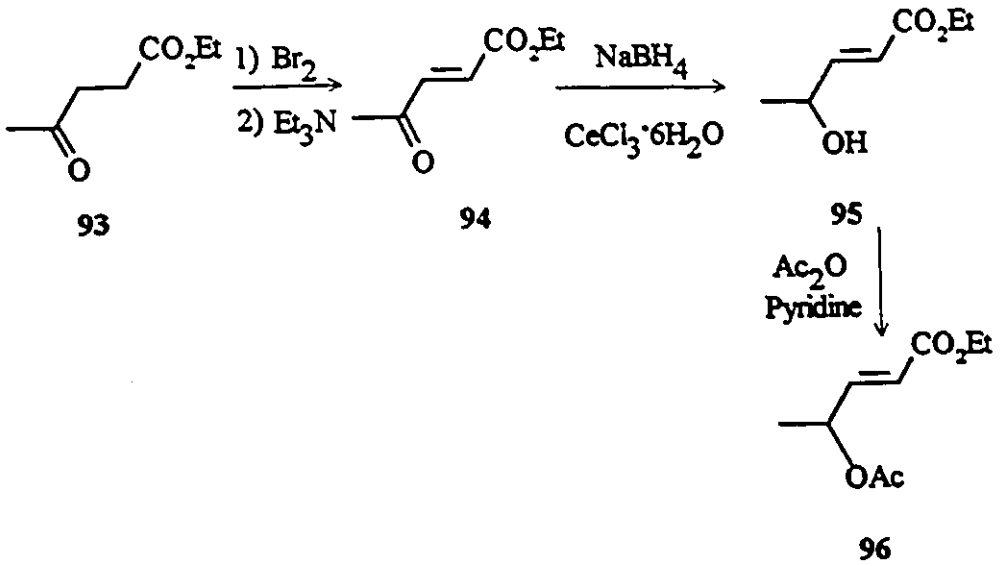
This study required γ-oxygenated α,β-unsaturated alkenoates as substrates and silyl ketene acetals and silyl enol ethers as nucleophiles. Two allylic acetates were chosen as substrates. The first, ethyl (*E*)-4-acetoxy-2-butenoate (**92**), was produced in 92% yield by refluxing ethyl-4-bromocrotonate in acetic acid in the presence of potassium acetate (Figure 28).[33] The second, ethyl (E)-hydroxy-2-pentenoate, was formed in three steps, beginning with ethyl levulinate. A bromination and subsequent elimination reaction was performed using triethylamine to produce the α,β-unsaturated keto ester **94** in 61% yield.[34] Reduction of the ketone to the alcohol was performed using sodium borohydride in the presence of cerium salts in 69% yield.[35] This was subjected to a standard acetylation with acetic anhydride and pyridine to produce **96** in 68% yield (Scheme 9).

Figure 28. Formation of ethyl (E)-4-acetoxy-2-butenoate



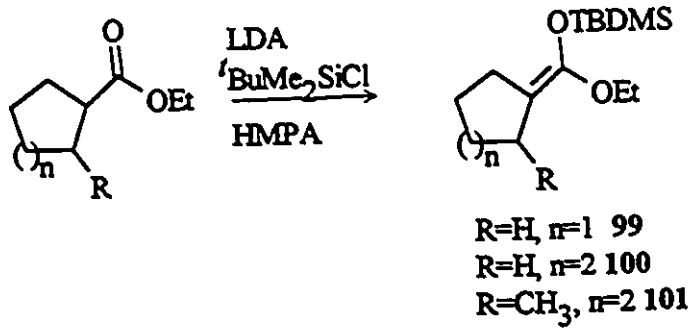
91 **92**

Scheme 9. Preparation of ethyl (E)-4-acetoxy-2-pentenoate

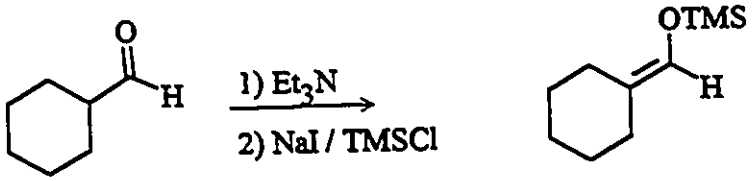


The ethyl esters employed for the synthesis of the nucleophiles were prepared by standard conditions from the corresponding carboxylic acids to produce compounds **97** and **98**. The cyclic silyl ketene acetals were formed using TBDMSCl due to the instability of those formed using TMSCl.[36a] They were synthesized from the corresponding ethyl ester by deprotonation with LDA and subsequent addition of *t*-butyldimethylsilyl chloride in the presence of HMPA.[36b] The silyl enol ether was prepared by addition of the aldehyde to triethylamine in the presence TMSI formed *in situ* (Figure 29).[36c]

Figure 29. The synthesis of silyl enol ethers and silyl ketene acetals



R=H, n=1 **99**
R=H, n=2 **100**
R=CH_3, n=2 **101**



102

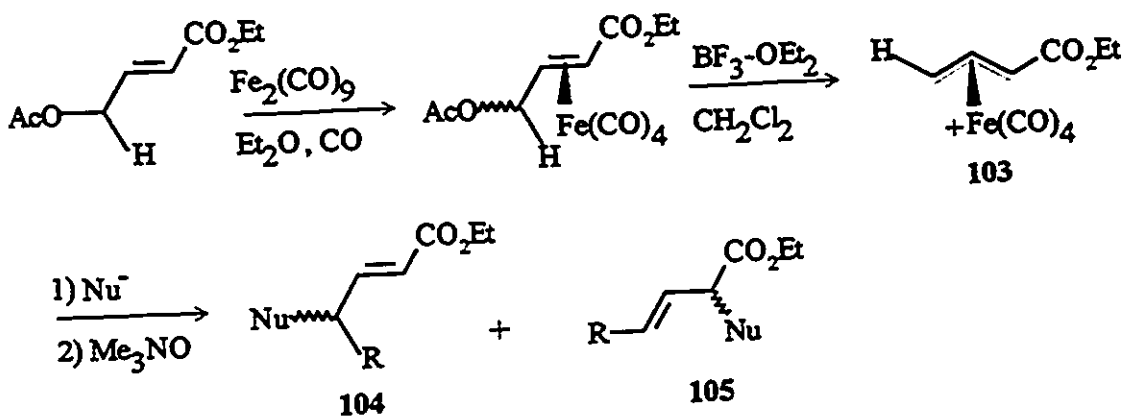
The addition of the Lewis acid then formed the η^3-tetracarbonyliron complex, which reacted with the nucleophile to produce the condensation products. The Lewis acid chosen for this purpose was BF_3-OEt_2, based on earlier reports indicating this to be superior to other Lewis acids for cation formation.[28c] The existence of cation **103** has been shown in earlier work by low temperature ^{1}H NMR studies.[28b]

Decomplexation of the condensation products was accomplished using trimethylamine N-oxide.[28b] In earlier studies on less substituted cases, this type of decomplexation was complete in a few hours.[28b,c] In these cases, a 24-48 h period was required to accomplish the decomplexation. This may be due to the presence of a quaternary centre in the homoallylic position. The crude reaction products were initially

purified by bulb to bulb distillation, which removed the residual iron. Generally, column chromatography was performed subsequently, to remove any remaining starting materials.

Spectroscopic studies provided conclusive evidence that the nucleophiles had entered in the position γ–with respect to the ester function, producing the homologous (1,5)-Michael addition products (**104**) as opposed to regioisomerically functionalized products (**105**) (Figure 30). For compound **106**, the presence of absorptions of the vinyl protons at δ 6.84 and 5.76 in the ^{1}H NMR spectrum, and the absorptions at the vinyl carbons at δ 144.1 and 124.0 in the ^{13}C NMR, identify it as an α,β-unsaturated carbonyl compound **104**. Further evidence for this was present in the ^{13}C NMR spectrum which revealed a resonance peak at 166.2 ppm for the ester carbonyl, also indicating a conjugated ester function.

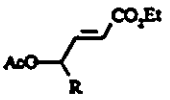
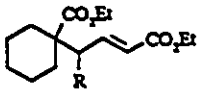
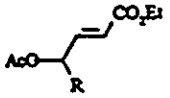
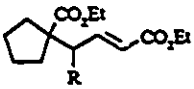
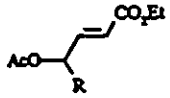
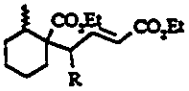
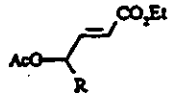
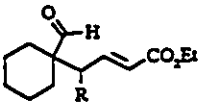
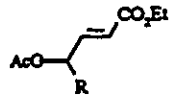
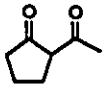
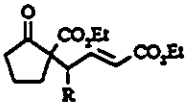
Figure 30. Procedure for iron allyl tetracarbonyl addition reactions



In all cases studied, the stereochemistry of the double bond was retained in the product which is consistent with the known geometric stability of iron allyl tetracarbonyl

cationic complexes. The geometry of the double bond was identified by the coupling constants of the vinyl protons which were all close to 15 Hz, indicating a *trans* double bond. Also, the nucleophile was found to attack at the terminus remote from the ester function. In no case, was any product from nucleophilic addition in the α-position obtained; this corresponds with earlier results reported.[28] The results of the homologous (1,5)-Michael reaction are shown in the table below.

Table 1. The results of the homologous (1,5)-Michael with substrate

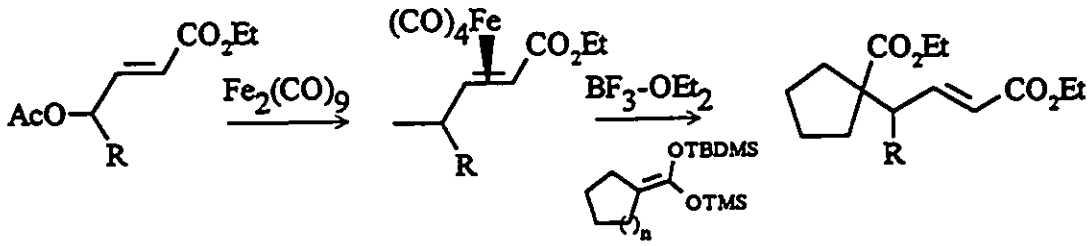
Substrate	Nucleophile	Product	Yield
 R=H 92, R=CH$_3$ 96	100	 R=H 106 R=CH$_3$ 107	106 72% 107 66%
 R=H 92, R=CH$_3$ 96	99	 R=H 108 R=CH$_3$ 109	108 66% 109 63%
 R=H 92, R=CH$_3$ 96	101	 R=H 110 R=CH$_3$ 111	110 46% 111 51%
 R=H 92, R=CH$_3$ 96	102	 R=H 112 R=CH$_3$ 113	112 74% 113 68%
 R=H 92, R=CH$_3$ 96		 R=H 114 R=CH$_3$ 115	114 47% 115 41%

As the table indicates, the yields ranged from 41-74%. In the case of compounds **110, 114** and **115**, starting material was recovered. A general trend can be seen in

comparing the yields produced by employing the two substrates **92** and **96**. The reactions which utilized methyl-substituted substrate **96** produced the γ-substitution product in lower yields than those with substrate (**92**). This is most likely due to the steric hindrance between this methyl group and the incoming nucleophile. The nucleophile employed also has a large effect on the the yield of the reaction. The use of the β-keto ester as a nucleophile produced the lowest yields. This is attributed to the lack of activation of the nucleophile since the reactivity is due to an equilibrium concentration of the enol which is less than 100%. In order to improve the nucleophilicity of this compound, a base should be employed or the silyl enol ether prepared.

The yields produced were, on average, lower than those produced in an earlier investigation of nucleophilic additions to α,β-unsaturated esters.[28c] In this case however, quaternary centres were produced. This is the first instance in which an iron allyl cation has been used to form a quaternary centre (Figure 31).

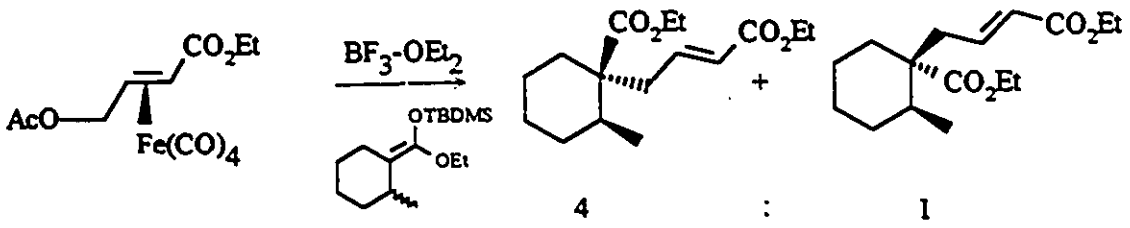
Figure 31. The formation of quaternary centres



The formation of compound **110** occurs in a diastereomeric mixture of 4:1. The ratio of diastereomers was determined by ^{1}H NMR integration, using the two methyl doublets. The mixture could not be separated by column chromatography and the major

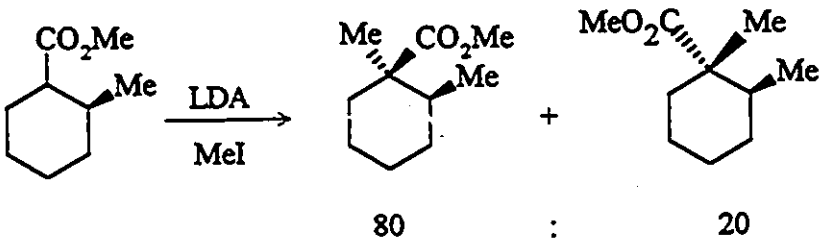
diastereomer was therefore identified on the basis of literature analogy. It was assumed that the major diastereomer is that which is formed by nucleophilic attack with the methyl group on the nucleophile orientated away from the reactive site (Figure 32).

Figure 32. The formation of a 4:1 diastereomeric mixture



This assumption is supported by an earlier investigation of alkylation of enolates. It was reported that compound exhibits alkylation *anti* to the methyl substituent [37] (Figure 33).

Figure 33. Alkylation of methyl substituted enolates

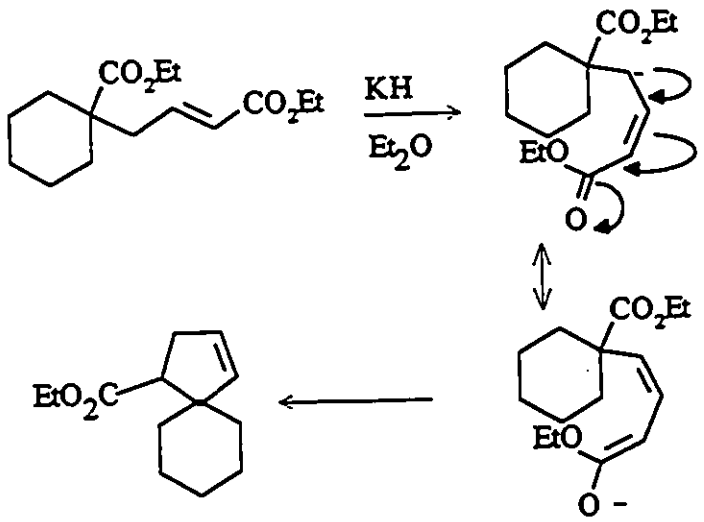


Compound **115** was also isolated as a mixture of two diastereomers, in a ratio of 2:1. These could be partially separated by column chromatography to provide the major isomer in diastereomerically pure form. The diastereomeric ratio was determined by ^{1}H

NMR using the methyl doublets in the crude reaction products. Compound **111** was also isolated as a mixture of many diastereomers. No effort was made, in this case, to identify any of the diastereomers.

Once the iron allyl adducts were produced in moderate to good yields, attention was turned to the spirocyclization reactions. The first method chosen for this was the Dieckmann condensation,[38] which would produce a five membered ring. Although the substrates produced in the iron allyl cation condensation reaction contain an *E* double bond, it was thought that removal of a proton in the γ-position would form the *cis* dienolate, which would allow formation of the ring (Scheme 10). The formation of *cis* dienolates in preference to *trans* from *trans* alkenoates is well documented.[39]

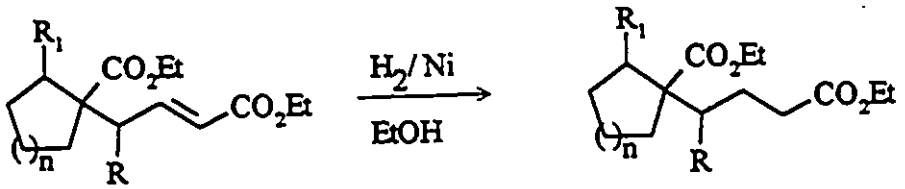
Scheme 10. The formation of *cis* dieneolates



This rationale was not borne out by experiment. Although the Dieckmann was attempted on **106** under a variety of conditions, in no circumstance was the spirocycle produced. In most cases, an unidentifiable mixture of products was recovered. In order

to eliminate this problem, the C=C double bond was removed by catalytic hydrogenation. This was performed using Raney® nickel in ethanol, which produced the alkyl diesters **116-119** in good yield (Figure 34).

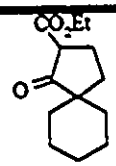
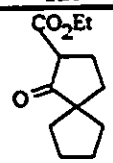
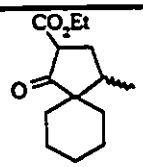
Figure 34. Hydrogenation of iron allyl adducts



116 R=H, R_1=H, n=1 (80%)
117 R=H, R_1=H, n=2 (79%)
118 R=H, R_1=CH_3, n=2 (87 %)
119 R=CH_3, R_1=H, n=2 (80 %)

The Dieckmann was again attempted, this time with the hydrogenated compound **117**. The reaction was successful, as the spirocyclic ester was formed in good yield. The reaction was attempted using two other diesters (**116, 119**) (Table 2).

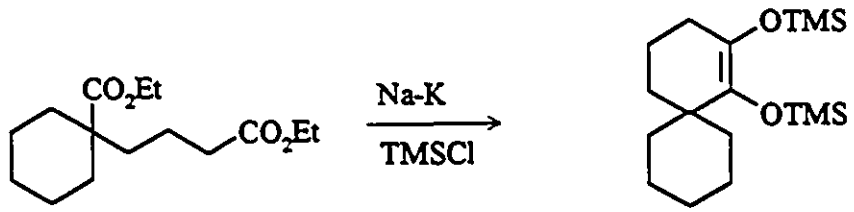
Table 2. Results of the Dieckmann condensation

Compound	Product	Yield
117	 **120**	80%
116	 **121**	79%
119	 **122**	80%

After realizing success with the Dieckmann condensation, other cyclization methods were attempted in order to vary the size of the newly formed ring. The acyloin condensation[40] will allow the ring closure to produce a six membered ring, and thus was the next reaction studied. When this reaction was first attempted on the iron allyl addition product **106**, prior to hydrogenation, no acyloin product was formed. The reaction products from the iron allyl addition reaction were again hydrogenated before being employed in the reaction. After several failures using a variety of conditions, success was achieved using a sodium-potassium alloy in conjunction with chlorotrimethylsilane (TMSCl).[40] The chlorotrimethylsilane prevents the competing Dieckmann reaction from

occurring[40] and is generally is reported to raise yields in acyloin condensations [41] (Figure 35).

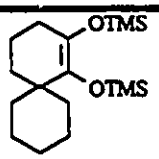
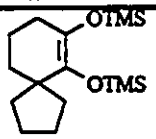
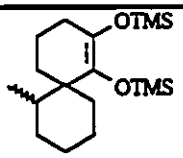
Figure 35. The acyloin condensation



117 **122**

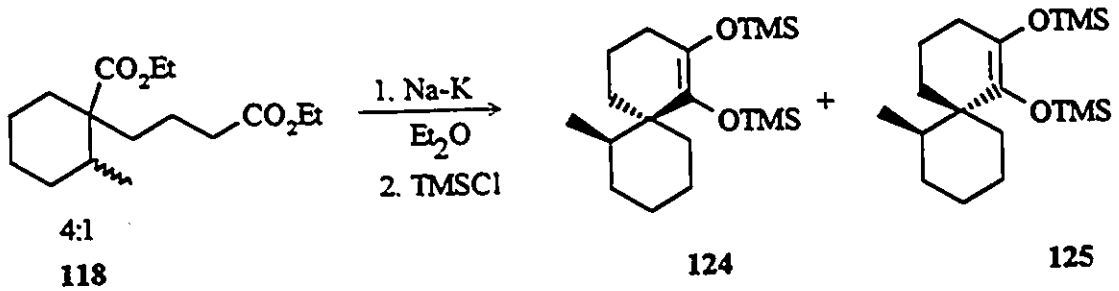
After the initial success using compound **117**, the reaction was attempted using two other substrates (**116**, **118**). The results are shown in Table 3.

Table 3. The results of the acyloin condensation

Substrate	Product	Yield
117	 **122**	85%
116	 **123**	47%
118	 **124, 125**	43%

In all cases, the product was easily purified by column chromatography. Methyl substituted starting material **118**, isolated from the iron allyl addition reaction as a 4:1 diastereomeric mixture, gave a 4:1 mixture of diastereomeric bis (trimethylsilyloxy)ethers **124** and **125**.

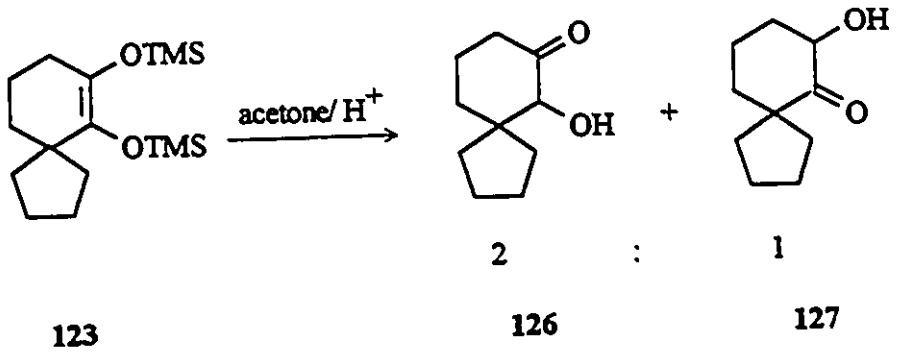
Figure 36. The acyloin condensation using a 4:1 diastereomeric mixture



The major diastereomer, **124**, could be separated by preparative TLC; the relative stereochemistry of its two chiral centres was assigned by correllation with the major diastereomer of starting **118**. Due to the suspected sensitivity of these compounds, distillation was not performed. The products were easily identified by their ^{1}H and IR spectra. For compound **123** , the presence of the two trimethylsilyl groups at δ 0.17 and 0.15 in the ^{1}H NMR spectrum of **116** and the disappearance of the strong carbonyl stretches at 1738 and 1726 cm^{-1} in the IR spectrum identified it as the acyloin product.

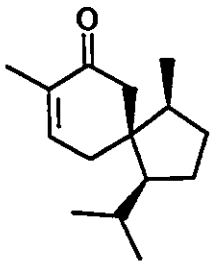
The trimethylsilyl groups were removed from compound **123** by stirring in an acidic environment. The product however, was obtained in low yield as a 2:1 mixture of regioisomers **126** and **127** (Figure 37).

Figure 37. The removal of trimethylsilyl groups



A new method of spirocyclization was employed in order to find conditions which would allow the synthesis of the ring system of the natural product acorenone (Figure 38).

Figure 38. Acorenone

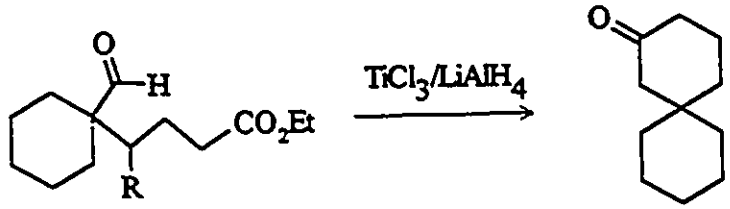


128

The McMurry coupling reaction was chosen for this purpose (Figure 39). The McMurry reaction couples two carbonyl functions to produce an alkene and is well documented for ketone-ketone coupling.[42] Ketone-ester coupling has also been achieved by this reaction.[43] The compound which was employed as the substrate in this reaction is the ester-aldehyde (112). In this case, the product should be a ketone. Before attempting

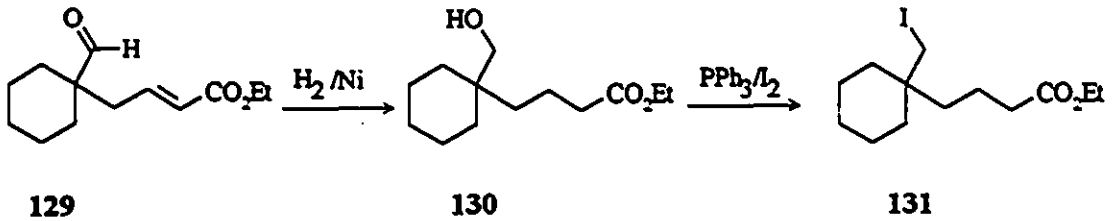
this reaction, the compound was partially hydrogenated to remove the double bond. This product was not stable and could not be stored for more than a few days. The compound was also extremely acid sensitive and would produce a white solid upon contact which was presumed to be a polymer. The McMurry reaction was attempted under a variety of conditions[43,44] but all cases proved unsuccessful. In most cases, an unidentifiable mixture of multiple compounds was obtained.

Figure 39. The McMurry coupling reaction



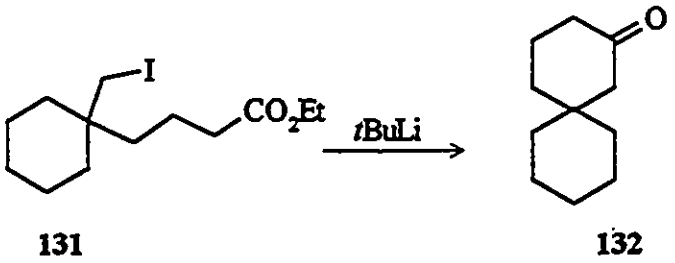
After many attempts at the McMurry reaction, an alternative route to this ring system was explored. The route selected involved cyclization by metal-halogen exchange and subsequent nucleophilic attack on the ester by an organolithium.[45] Compound **131** was prepared for this purpose by fully reducing the ester-aldehyde to form the alcohol, **130**,in 80% yield. This was iodinated using triphenylphosphine and iodine[46] to produce the iodide, **131**, in 87% yield (Figure 40).

Figure 40. Preparation of the iodinated alkyl ester



The iodinated compound **131** was lithiated with the hope that spirocyclization would occur. Addition of compound **131** to ^{t}BuLi produced a mixture of products. The spirocycle **132** was formed, however, in low yield and was accompanied by a mixture of products. The iodine atom is positioned on a neopentyl centre which may slow lithiation and consequently lower the yield. There are several alternatives which remain to be investigated,[47] but due to time constraints, the metal-halogen exchange pathway has been left at this stage of completion.

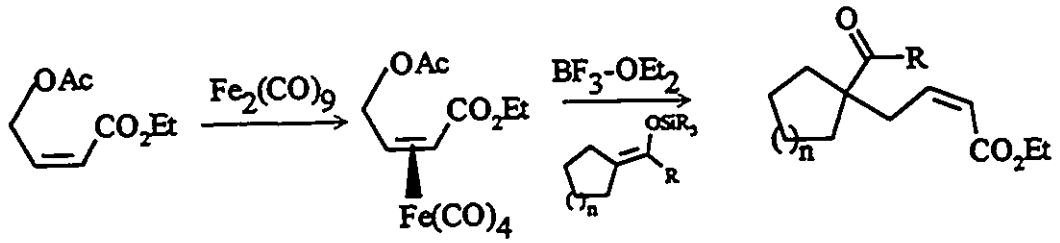
Figure 41. Spirocyclization by metal-halogen exchange



FUTURE WORK

The iron allyl addition reaction of α,β-unsaturated esters has proven itself useful in the formation of quaternary centres and as the central feature in a short route to spirocyclic ring systems. It would be useful however, to be able to spirocyclize with the iron allyl adducts prior to hydrogenation. The coupling may be more likely to occur if the alkene is in the *Z* configuration. If the starting alkene is *Z*, the geometric stability of the iron allyl cation should provide the *Z* addition product. This should allow for facile ring closure as the double bond would already be in the appropriate configuration (Figure 42). Future work on this project should include attempting the iron allyl addition reaction using the Z configuration of the substrates **92** and **96** and subsequent cyclization by each of the methods discussed.

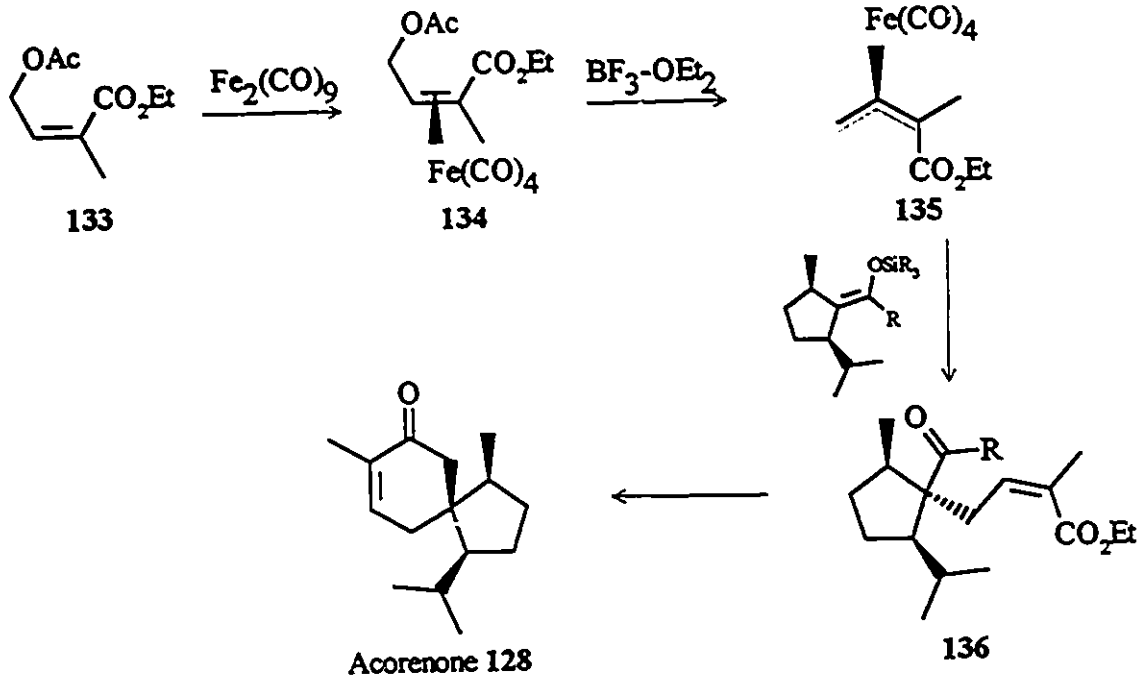
Figure 42. Iron condensation reaction using *Z* substrates



There are a wide variety of natural products containing a spirobicyclic ring system. The spiro[4.5]decanes are an important class of spirocyclic sesquiterpenes as they have been used as antifungal agents.[10] A versatile method which would allow for the synthesis

of spirocycles containing a wide variety of functional groups would be extremely useful. One of the compounds in this class is acorenone. The allyl iron condensation chemistry could allow for the ready synthesis of this natural product (Scheme 11).

Scheme 11. Proposed synthesis of acorenone.



The final step of this reaction sequence requires the coupling of two carbonyl compounds. As shown earlier, the ring could be closed using lithiation, however, the yield was very low for this reaction. The McMurry coupling reaction did not provide any product for the aldehyde esters studied. This was thought to be due in part, to the harsh reaction conditions which are required. Other types of coupling reactions may provide the

same transformation as the McMurry, but with milder conditions. Low valent tungsten halides and carbonyls have been used to couple aldehydes and ketones at room temperature to afford alkenes.[47] This may be worth investigating using the ester aldehyde compound. Also, a Grignard reaction could be attempted on the iodinated compound to close the ring. If the alkene does not cyclize, the double bond may be introduced after cyclization by an elimination reaction.

CONCLUSION

The homologous-(1,5) Michael reaction using γ-acetoxy-α,β-unsaturated esters provides a useful method of forming quaternary centres. The addition of cyclic nucleophiles provides products which are precursors to spirocyclic ring systems. The products can be spirocyclized using the acyloin and the Dieckmann condensation reactions in moderate to good yields. In these cases, the product must first be hydrogenated to remove the double bond. The addition products can also be cyclized by lithiation after hydrogenation and subsequent iodination, but in low yield. This type of chemistry could allow for the synthesis of the ring systems of natural products such as acorenone-B.

Chapter Three

EXPERIMENTAL

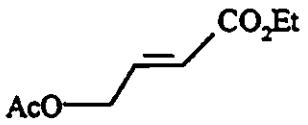
General Information

Nuclear magnetic resonance spectra were run on a Bruker AC Spectrometer at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C in $CDCl_3$ solution at 25 °C. Infrared spectra of liquids were run as neat samples between potassium bromide plates on a Bomem Michelson 100 spectrometer. Mass spectra were run on a Kratos Profile mass spectrometer on electron impact mode. High resolution mass spectra were within 5 ppm of the expected value. Analytical thin layer chromatography was performed using Merck precoated silica gel 60 F_{254} aluminum sheets. Preparative thin layer chromatography was performed using Analtech silica gel GF* 1000μm plates. "Flash chromatography" was performed as described by Still[48] using 60 (70-230) mesh silica gel.

Diethyl ether (Et_2O) and tetrahydrofuran were distilled from benzophenone-ketyl prior to use. Dichloromethane and acetonitrile were distilled from calcium hydride prior to use. All distillations took place under a nitrogen or argon atmosphere. The phrase "conventional workup" refers to extraction of the reaction product with diethyl ether or dichloromethane, drying of the combined organic layers using magnesium sulphate followed by filtration and evaporation of the solvent under reduced pressure to afford the crude product. Pure products were obtained using bulb to bulb distillation and/or chromatography.

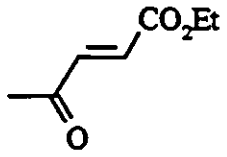
For the iron allyl addition reactions, the η^2-iron tetracarbonylalkene complexes were used immediately after preparation without purification or characterization. The Lewis acid, BF_3-OEt_2 was used after distillation under nitrogen. All reactions were performed under a nitrogen or argon atmosphere unless noted otherwise. Diastereomeric ratios were determined by integration of the ^{1}H NMR resonances.

Ethyl (*E*)-4-acetoxy-2-butenoate (92)



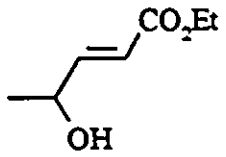
Ethyl (*E*)-4-acetoxy-2-butenoate was prepared by the method of Leonard and Felley[33] (92%).bp 60 °C/ 0.42 torr, lit. bp 61 °C-63 °C/0.5 torr.

Ethyl (*E*)-4-oxo-2-pentenoate (94)



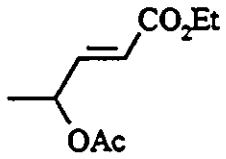
Ethyl (*E*)-4-oxo-2-pentenoate was prepared by the method of McMurry and Blaszczak[34] (61%) bp 70 °C/0.25 torr, lit bp[34] 65 °C/0.2 torr.

Ethyl (*E*)-4-hydroxy-2-pentenoate (95)



To $CeCl_3$–$6H_2O$ (13.1 mmol, 4.620 g) in ethanol (25 mL) was added ethyl (*E*)-4-oxo-2-pentenoate (1.860 g , 13.1 mmol) followed by $NaBH_4$ (0.540 g , 14.4 mmol). The resultant mixture was allowed to stir for 5 minutes and subjected to a conventional workup. The crude product was subjected to a bulb to bulb distillation (125 °C/0.44 torr) to afford ethyl (*E*)-4-hydroxy-2-pentenoate (1.300 g, 69%), lit. bp[49] 115°C/ 0.1 torr.

Ethyl (*E*)-4-acetoxy-2-pentenoate (96)

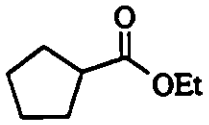


Ethyl (*E*)-4-hydroxy-pentenoate (3.620 g, 25.2 mmol) and acetic anhydride (15 mL) were mixed in a two neck flask and cooled in ice. Pyridine (2 mL) was added and the resultant mixture was allowed to stir overnight. A conventional workup was performed and the crude product was purified by bulb to bulb distillation (100 °C/1.0 torr) to yield ethyl (*E*)-4-acetoxy-2-pentenoate (3.200 g, 68%)[28c]. Compound 96 was identified spectroscopically, IR: 2984, 1740, 1725, 1662, 1237cm^{-1}; ^{1}H NMR: δ 6.84 (d of d, 1H, J=15.6 Hz, J=4.95), 5.93 (d, 1H, J=15.6), 5.46 (m, 1H), 4.18 (q, 2H, J=7.1), 2.06 (s,

3H), 1.34 (d, 3H, J=6.7Hz), 1.27 (t, 3H, J=7.1Hz);^{13}C NMR: δ 170.1, 166.2, 146.3, 121.1, 68.9, 60.7, 21.2, 19.7, 14.2.

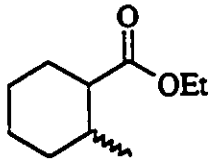
General procedure for the formation of ethyl esters. Procedure (I)

Ethyl cyclopentanecarboxylate (97)



Cyclopentane carboxylic acid (9.500 g, 83.1 mmol) was added to EtOH (60 mL) followed by 8 drops of concentrated sulphuric acid. The mixture was allowed to reflux overnight. A conventional workup was performed and the crude product was purified by bulb to bulb distillation (70 °C/28 torr) to afford ethyl cyclopentanecarboxylate (9.510 g, 81%), lit. bp^{50} 89.3 °C/45 torr.

Cis and *trans* Ethyl 2-methylcyclohexanecarboxylate (98)

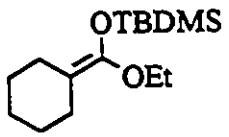


Subjecting 2-methyl cyclohexanecarboxylic acid (2.000 g, 14.1 mmol) to procedure (I) produced ethyl 2-methylcyclohexanecarboxylate (2.430 g, 84%). The

product was purified by bulb to bulb distillation (55 °C/0.58 torr), lit. bp[51] 50.97 °C/10 torr.

General procedure for the preparation of silyl ketene acetals. Procedure (II)

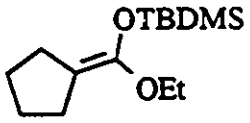
[(*t*-Butyldimethylsiloxy) ethoxymethylene]cyclohexane (**100**)



To diisopropylamine (2.12 mL, 21.0 mmol) was added dry tetrahydrofuran (15 mL) and the mixture was cooled to -78 °C in a dry ice/acetone bath. *n*-BuLi (11 mL, 1.91 M, 21.0 mmol) was added and the mixture was allowed to stir for five minutes. The cooling bath was removed and the mixture was allowed to stir for an additional five minutes. The reaction was again immersed in a dry ice/acetone bath and ethyl cyclohexanecarboxylate (2.967 g , 19.0 mmol) was added. The mixture was allowed to warm to 0 °C, at which time HMPA (1.5 ml) was added. The mixture was allowed to stir for 15 minutes at 0 °C. A solution of TBDMSCl (3.165 g , 21.0 mmol) in 10 mL of THF was added and the mixture was allowed to warm to room temperature, at which time it was quenched with cold water and subjected to a conventional workup to afford the crude product. The product was purified by bulb to bulb distillation (80 °C/0.5 torr) to yield **100** (4.217 g , 84%). Compound **100** was identified spectroscopically, IR: 2931, 2857, 1700, 1452, 1251, 1177, 840, 781 cm^{-1}; ^1H NMR: δ 3.74 (q, J=7.1Hz, 2H), 2.10-1.65 (m,10H),

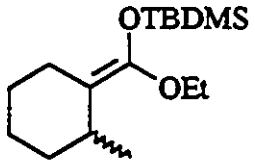
1.19 (t, J=7.1Hz, 3H), .924 (s, 9H), .114 (s,6H); ^{13}C NMR: δ 146.2, 100.6, 65.2, 27.8, 27.3, 27.2, 27.1, 26.9, 25.8, 18.2, 14.8, -4.6; MS: m/z 270 (M+); HRMS: calculated for $C_{15}H_{30}O_2Si$ 270.2015 (M+), found 270.2018.

[(t-Butyldimethylsiloxy)ethoxymethylene]cyclohexane **(99)**



Subjecting ethyl cyclopentanecarboxylate (2.953 g , 23.1 mmol) to procedure (II) followed by bulb to bulb distillation (95 °C/3.0 torr) produced **99** (2.063 g, 79%). Compound **99** was identified spectroscopically, IR: 2954, 2932, 2859, 1710, 1472, 1078, 1031, 839, 782; ^{1}H NMR:δ 3.78 (q, 2H, J=7.1), 1.21 (t, 3H, J=7.1) 2.18-1.54 (m, 8H), .921 (s, 9H), .120 (s, 6H); ^{13}C NMR: δ 146.3, 102.3, 64.5, 28.4, 27.8, 27.1, 26.9, 25.7, 18.0, 15.1, -4.5; MS: m/z 256 (M+); HRMS: calculated for $C_{14}H_{28}O_2Si$ 256.1859 (M+), found 256.1864.

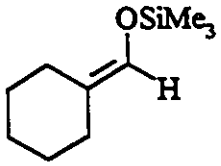
[(*t*-Butyldimethylsiloxy)ethoxymethylene]-2-methylcyclohexane **(101)**



Subjecting compound **98** (1.520 g, 8.98 mmol) to procedure (II) afforded the silyl ketene acetal (1.701 g, 66%), which was purified by bulb to bulb distillation (80 °C/2.6 torr). Compound **101** was identified spectroscopically, IR: 2960, 2930, 2858, 1684,

1472, 1463, 1444, 1389, 1362, 1259, 1090, 1067, 1101, 841, 811, 687 cm^{-1}; ^1H NMR: δ 3.73 (q, 2H, J=7.0), 1.86-1.46 (m, 9H), 1.19 (t, 3H, J=7.0), 0.99 (d, 3H, J=7.1), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR:145.9, 104.0, 65.4, 2.8, 28.3, 28.2, 25.7, 25.5, 22.4, 21.0, 17.8, 14.8, -4.7MS: m/z 284 (M+); HRMS: calculated for $C_{16}H_{32}O_2Si$ 284.2172 (M+), found 284.2170.

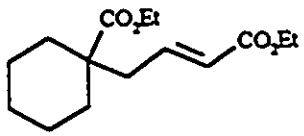
(Trimethylsiloxymethylene)cyclohexane **(102)**



Cyclohexanecarboxaldehyde (0.660 g, 6.00 mmol) and triethylamine (0.84 mL, 6.00mmol) were added to a 3-neck flask equipped with a reflux condenser and a pressure equalizing addition funnel. Trimethylchlorosilane (0.76 mL, 6.00 mmol) was added dropwise and after completion, the reaction was heated to 35 °C and allowed to stir for ten minutes, at which time sodium iodide (0.900 g, 6.00 mmol) in acetonitrile (25 mL) was added through the addition funnel. The reaction was then heated to 70 °C for two hours and quenched with cold water. A conventional workup was performed, followed by bulb to bulb distillation (70 °C/1.1 torr) to afford pure **102** (0.651 g, 60%).[52] Compound **102** was identified spectroscopically, IR: 2957, 2926, 2853, 1679, 1447, 1253, 1154, 1091, 933, 910, 874, 844 cm^{-1}; ^1H NMR: δ 5.97 (s, 1H), 2.17-1.45 (m, 10H), 0.138 (s, 9H); ^{13}C NMR: δ 130.2, 122.6, 30.7, 28.5, 27.1, 27.1, 25.4, -0.5; MS: m/z 184 (M+); HRMS: calculated for $C_{10}H_{20}OSi$ 184.1283 (M+), found 184.1287.

General Procedure for the Iron Allyl Cation Addition Reactions. Procedure (III)

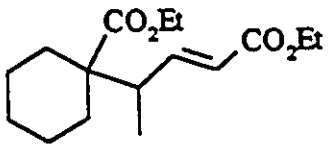
Ethyl (*E*)-4-(1-ethoxycarbonylcyclohexyl)-2-butenoate (**106**)



A mixture of $Fe_2(CO)_9$ (1.940 g, 5.34 mmol) and ethyl 4-acetoxycrotonate (0.657 g, 3.82 mmol) in dry diethyl ether was stirred under CO at room temperature for five hours. The reaction product was then filtered through Celite ® and concentrated under reduced pressure to yield a dark brown oil. The oil was redissolved in dry dichloromethane and the mixture was cooled to -78 °C. Compound **100** (1.140 g, 4.20 mmol) was added followed by $BF_3{\cdot}OEt_2$ (0.52 mL, 4.20 mmol). The reaction mixture was stirred for 12 h during which time it was allowed to warm to room temperature. The mixture was opened to the air and $NaHCO_3$ was added, followed by $Me_3NO{\cdot}2H_2O$ and acetone. After stirring overnight, 3M HCl was added and a conventional workup was performed. The crude product was purified by bulb to bulb distillation (93 °C/0.70 torr) followed by flash chromatography (10:1 petroleum ether: diethyl ether) to yield **106** (0.730 g, 72% yield). Compound **106** was identified spectroscopically, IR: 2935, 2857, 1723, 1657, 1452, 1207, 1163, 1097, 988 cm^{-1}; ^1H NMR: δ 6.84 (d of t, 1H, J=15.5, J=7.8), 5.76 (d, 1H, J=15.5), 4.14 (q, 2H, J=7.0),4.14 (q, 2H, J=7.0), 2.34 (d, 2H, J=7.8), 2.06-1.52 (m, 10H) , 1.27 (t, 3H, J=7.0), 1.27 (t, 3H, J=7.0) ;^{13}C NMR: δ 175.7,

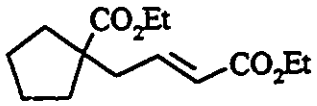
166.2, 144.1, 124.0, 60.4, 60.3, 47.1, 42.5, 33.9, 25.7, 23.1, 14.3; MS: m/z 268, (M+); HRMS: calculated for $C_{15}H_{24}O_4$ 268.1675 (M+), found 268.1663.

Ethyl (*E*)-4-(1-ethoxycarbonylcyclohexyl)-4-methyl-2-butenoate **(107)**



Procedure (III) was followed using ethyl 4-acetoxy-2-pentenoate, **96**, (0.511 g, 2.74 mmol). After decomplexation, the crude product was subjected to bulb to bulb distillation (88 °C/ 0.60 torr) and further purified by flash chromatography (10:1 petroleum ether:diethyl ether) to yield pure **107** (0.508 g, 66%). Compound **107** was identified spectroscopically, IR: 2978, 2935, 2859, 1721, 1652, 1452, 1368, 1264, 1201, 1133, 1028, 984 cm^{-1}; ^1H NMR: δ 6.84 (d of d, 1H, J=15.6, J=8.2), 5.71 (d, 1H, J=15.6), 4.11 (q, 2H, J=6.9), 4.09 (q, 2H, J=7.0), 2.36-1.01(m, 17H), 0.94 (d, 3H, J=8.2); ^{13}C NMR: δ 175.0, 166.5, 150.2, 122.0, 60.3, 60.3, 50.3, 45.4, 32.6, 31.2, 25.8, 23.6, 23.4, 14.8, 14.4; MS: m/z 282, (M+); HRMS: calculated for $C_{16}H_{26}O_4$ 282.1831 (M+), found 281.9771.

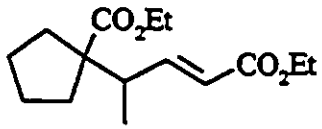
Ethyl (*E*)-4-(1-ethoxycarbonylcyclopentyl)-2-butenoate **(108)**



Ethyl 4-acetoxy-2-butenoate , **92** , (0.653 g, 3.793 mmol) was subjected to procedure (III), replacing compound **100** with compound **99** (1.070 g, 4.172 mmol) to

provide the crude product. Bulb to bulb distillation, (90 °C/0.35 torr) followed by flash chromatography, (10:1 petroleum ether:diethyl ether) provided ethyl (E)-4-(1-ethoxycarbonylcyclopentyl)-2-butenoate, **108**, (0.632 g, 66%) as a clear, colourless liquid. IR: 2958, 2873, 1723, 1651, 1268, 1178, 1121, 1098, 1041, 980, 863, 712 cm^{-1}; ^{1}H NMR: δ 6.78 (d of t, 1H, J=15.5, J=7.7), 5.75 (d,1H, J=15.5), 4.08 (q, 2H, J=7.1), 4.08(q, 2H, J=7.1), 2.47 (d, 2H, J=7.7), 2.10-1.23 (m, 8H), 1.20 (t, 3H, J=7.1), 1.17(t, 3H, J=7.1); ^{13}C NMR: δ 176.9, 166.4, 145.3, 123.8, 60.7, 60.3, 53.2, 41.0, 36.1, 25.2, 14.3. MS: m/z 254, (M+) ; HRMS: calculated for $C_{14}H_{22}O_4$ 254.1518 (M+), found 254.1512.

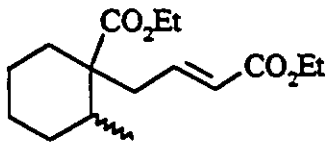
Ethyl (*E*)-4-(1-ethoxycarbonylcyclopentyl)-4-methyl-2-butenoate (**109**)



Subjecting ethyl 4-acetoxy-2-pentenoate (0.581 g, 3.124 mmol) to procedure (III), replacing compound **100** with compound **99** (0.880 g, 3.436 mmol) yielded pure **109** (0.519 g, 62%) after bulb to bulb distillation (90 °C/0.35 torr),and subsequent flash chromatography (2:1 petroleum ether:diethyl ether). Compound **109** was identified spectroscopically, IR: 2976, 2874, 1723, 1651, 1462, 1453, 1266, 1181, 1036, 982, 865, 726 cm^{-1} ;^{1}H NMR:δ 6.92 (q, 1H, J=15.6, 8.6), 5.78 (d, 1H, J=15.6), 4.11 (q, 2H, J=7.1), 4.16 (q, 2H, J=7.2), 2.65 (m, 1H), 2.14-1.36 (m, 8H), 1.25 (m, 6H, J=7.0), 1.00 (d, 3H, J=6.8); ^{13}C NMR: δ 176.5, 166.7, 150.7, 121.9, 60.7, 60.4, 57.7, 43.4, 34.6, 32.9, 25.3,

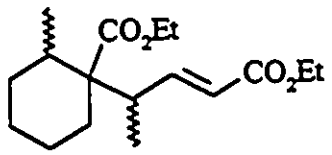
25.2, 16.0, 14.3; MS: m/z 268 (M+); HRMS:calculated for $C_{15}H_{24}O_4$ 268.1675 (M+), found 268.1665.

Ethyl (*E*)-4-(1-ethoxycarbonyl-2-methylcyclohexyl)-2-butenoate **(110)**



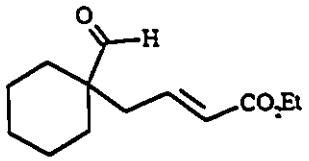
Compound **92** (0.365 g, 2.12 mmol) was subjected to procedure (III) replacing compound **100** with compound **101** (0.730 g, 2.54 mmol). The product was subjected to bulb to bulb distillation (93 °C, 0.70 torr) followed by purification by flash chromatography (10:1 petroleum ether: diethyl ether) to afford pure **110** (0.264 g, 46%) as a clear colourless liquid. Compound **110** was identified spectroscopically, IR: 2934, 2864, 1725, 1654, 1463, 1448, 1368, 1157, 1096, 1030, 868 cm^{-1}; ^1H NMR: δ major 6.82 (d of t, 1H, J=15.5, 7.7), major 5.80 (d, 1H, J=15.5), minor 5.83 (d, 1H, J=15.2), 4.14 (q, 2H, J=7.1), 4.12 (q, 2H, J=7.1), 2.55 (m, 2H), 1.85-1.21 (m, 15H), major 0.95 (d, 3H, J=6.9), minor 0.81 (d, 3H, J=6.9); ^{13}C NMR: δ 175.5, 166.3, 144.9, 124.2, 60.3, 60.2, 49.5, 39.4, 37.5, 29.8, 29.8, 23.1, 22.1, 16.6, 14.4, minor 146.1, 123.7, 31.0, 24.0, 21.4. MS: m/z 282, (M+), HRMS: calculated for $C_{16}H_{26}O_4$ 282.1831 (M+), found 282.1833.

Ethyl (*E*)-4-(1-ethoxycarbonyl-2-methylcyclohexyl)-4-methyl-2-butenoate (**111**)



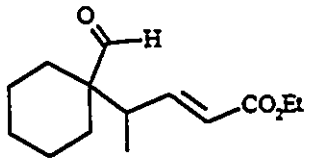
Compound **96** (0.205 g, 1.10 mmol) was subjected to procedure (III) replacing compound **100** with compound **101** (0.340 g, 1.21 mmol), to afford 1-ethyl carboxylate-1-(4-ethyl-1-methyl-2-butenoate)-2-methyl cyclohexane 0.167 g, 51%) as a mixture of diastereomers. Bulb to bulb distillation (90 °C/0.30 torr) followed by flash chromatography (10:1 petroleum ether: diethyl ether) afforded pure **111** as a diastereomeric mixture. Compound **111** was identified spectroscopically, IR: 2977, 2935, 2868, 1722, 1650, 1464, 1448, 1368, 1258, 1203, 1134, 1037, 868, 724 cm^{-1}; ^{1}H NMR: δ minor 7.07 (d of d, 1H, J=15.4, J=8.8), major 6.87 (d of d, 1H, J=15.7, J=9.1), other diastereomers obscured, major 5.84 (d, 1H, J=15.4), minor 5.71 (d, 1H, J=15.6), 4.15 (m, 4H), 3.00-1.15 (m, 16H), 0.95(m, 6H);^{13}C NMR: δ 174.8, 174.1, 166.6, 166.5, 151.2, 150.9, 149.9, 122.3, 121.6, 121.5, 60.4, 60.3, 60.1, 52.8, 52.4, 42.8, 40.0, 36.9, 34.4, 31.5, 31.0, 30.2, 30.0, 28.3, 27.5, 25.9, 24.8, 23.7, 22.7, 22.0, 19.4, 16.9, 16.5, 15.3, 15.1, 14.8, 14.4, 14.3, 14.1, 13.7; MS: m/z 296 (M+); HRMS: calculated for $C_{17}H_{28}O_4$ 296.1988 (M+), found 296.1989.

Ethyl (*E*)-4-[1-(oxomethyl)cyclohexyl]-2-butenoate (**112**)



Ethyl 4-acetoxycrotonate, (0.193 g, 1.12 mmol) was subjected to procedure (III) replacing compound **100** with compound **102**, (0.220 g, 1.23 mmol). The crude product was purified by bulb to bulb distillation (100 °C/1.1 torr) followed by flash chromatography (2:1 petroleum ether:diethyl ether) to produce pure **112** (0.186 g, 74%). Compound **112** was identified spectroscopically, IR: 2980, 2933, 2857, 1722, 1654, 1271, 1193, 1154, 1037, 986 cm^{-1}; ^{1}H NMR: δ 9.38 (s, 1H), 6.69 (d of t, 1H, J=15.5, J=7.8), 5.73 (d, 1H, J=15.5), 4.07 (q, 2H, J=7.2), 2.23(d, 2H, J=7.8), 2.07-1.15 (m, 13H); ^{13}C NMR: 205.8, 165.9, 143.1, 124.7, 60.3, 49.8, 38.4, 30.8, 25.4, 22.2,14.2; MS: m/z 224, (M+); HRMS: calculated for $C_{13}H_{20}O_3$ 224.1412 (M+), found 224.1405.

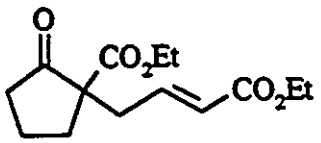
Ethyl (*E*)-4-[1-(oxomethyl)cyclohexyl]-4-methyl-2-butenoate (**113**)



Ethyl 4-acetoxy-2-pentenoate (0.782 g, 4.20 mmol) was subjected to procedure (III), replacing compound **100** with compound **102** (0.840 g, 4.62 mmol). Purification by bulb to bulb distillation (95 °C/0.50 torr) followed by flash chromatography (2:1

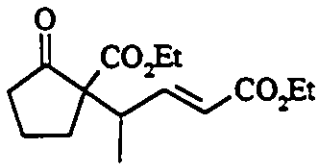
petroleum ether: diethyl ether) afforded pure **113** (0.620 g, 68%). Compound **113** was identified spectroscopically, IR: 2977, 2934, 2855, 2698, 1721, 1652, 1451, 1368, 1265, 1186, 1035, 985, 867, 742 cm^{-1}; ^{1}H NMR: δ 9.13 (s, 1H), 6.93 (d of d, 1H, J=9.3), 5.75 (d, 1H, J=15.6), 4.03 (q, 2H, J=7.1), 1.88-.63(m, 17H); ^{13}C NMR: δ 205.2, 165.8, 148.7, 122.8, 60.0, 51.8, 42.5, 29.9, 27.8, 25.4, 22.9, 22.6, 14.0, 13.7; MS: m/z 238, (M+) ; HRMS: calculated for $C_{14}H_{24}O_3$ 238.1569 (M+), found 238.1572.

Ethyl (*E*)-4-(1-ethoxycarbonyl-2-oxocyclopentyl)-2-butenoate (**114**)



Subjecting compound **92** (0.330 g, 7.70 mmol) to procedure (III), using ethyl-1-oxo-2 cyclopentanecarboxylate (1.330 g, 8.55 mmol) in place of compound **100**, produced compound **114**. Purification was accomplished by bulb to bulb distillation (95 °C/0.80 torr), followed by flash chromatography (5:3 petroleum ether:ethyl acetate) (0.893 g, 47%). Compound **114** was identified spectroscopically, IR: 2980, 1749, 1722, 1654, 1369, 1267, 1227, 1181, 1042, 861 cm^{-1}; ^{1}H NMR: δ 6.76 (d of t, 1H, J=15.5, J=7.6), 5.83 (d, 1H, J=15.5), 4.12 (q, 2H, J=7.1), 4.12 (q, 2H, J=7.1), 2.82-1.85 (m, 8H), 1.22 (m, 6H); ^{13}C NMR: δ 213.9, 170.5, 166.0, 143.1, 125.2, 61.6, 60.5, 59.5, 37.9, 36.0, 32.5, 19.6, 14.3, 14.1; MS: m/z 268, (M+); HRMS: calculated for $C_{14}H_{20}O_5$ 268.1311 (M+), found 268.1302.

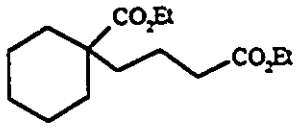
Ethyl (*E*)-4-(1-ethoxycarbonyl-2-oxocyclopentyl)-4-methyl-2-butenoate (**115**)



Compound **96** (0.528 g, 2.84 mmol) was subjected to procedure (III), using ethyl-1-oxo-2-cyclopentanecarboxylate (2.220 g, 14.2 mmol) in place of compound **100**. The crude reaction product was purified by bulb to bulb distillation (95 °C/0.80 torr) followed by flash chromatography (5:3 petroleum ether:ethyl acetate) to provide compound **115** as a mixture of diastereomers (2:1), (0.330 g, 41%). Compound **115** was identified spectroscopically, IR: 2979, 2905, 1754, 1722, 1652, 1465, 1368, 1226, 1179, 1111, 1023, 861 cm^{-1}; ^{1}H NMR: δ major 6.75 (d of d, 1H, J=15.5, J=8.0), minor 6.72 (d of d, 1H, J=15.5, J=7.8), major 5.79 (d, 1H, J=15.5), minor 5.78 (d, 1H, J=15.5), 4.14 (q, 2H, J=7.2 Hz), 4.10 (q, 2H, J=7.0), 3.23 (m, 1H), 2.43-1.84 (m, 6H), 1.22 (t, 3H, J=7.2), 1.19 (t, 3H, J=7.0), minor 1.02 (d, 3H, J=6.7), major 0.95 (d, 3H, J=6.9); ^{13}C NMR:major 213.6, 169.6, 166.3, 148.7, 122.6, 63.9, 61.9, 60.4, 39.9, 38.9, 28.6, 19.7, 14.8, 14.3, 14.1, minor-213.4, 169.3, 166.3, 148.0, 123.4, 64.6, 39.8, 28.7, 15.0; MS: m/z 282, (M+); HRMS: calculated for $C_{15}H_{22}O_5$ 282.1467 (M+), found 282.1471.

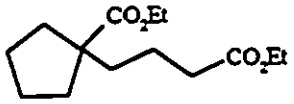
General Procedure for Hydrogenations. Procedure (IV)

2-Ethyl (*E*)-4-(1-ethoxycarbonylcyclohexyl)-butanoate (**117**)



Compound **106** (0.526 g, 1.96 mmol) was added to ethanol (15 mL). Raney® nickel was added and the mixture was allowed to stir under a hydrogen atmosphere at room temperature overnight. The Raney® nickel was then removed by filtration through Celite® and the filtrate was concentrated under reduced pressure. The crude product was subjected to a bulb to bulb distillation (bp 95 °C/0.90 torr) (lit. bp[53] 110-125 °C/0.7 torr) to yield pure **117** (0.422 g, 80%). ; IR: 2934, 2856, 1728, 1452, 1372, 1161, 1132, 1027, 932cm^{-1}; ^{1}H NMR:δ 4.09 (m, 4H), 2.20 (t, 2H, J=6.6), 2.04-1.12 (m, 20H); ^{13}C NMR: δ 176.6, 173.4, 60.3, 60.1, 46.7, 39.8, 34.7, 34.1, 26.0, 23.2, 19.8, 14.4, 14.3; MS: m/z 270, (M+); HRMS: calculated for $C_{15}H_{26}O_4$ 270.1831 (M+), found 270.1834.

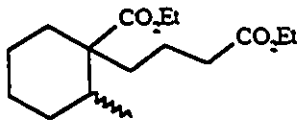
Ethyl (*E*)-4-(1-ethoxycarbonylcyclopentyl)-2-butanoate (**116**)



Subjecting compound **108** (0.272 g, 1.07 mmol) to procedure (IV) provided pure **116** (0.217 g, 79%) after bulb to bulb distillation (bp 95 °C/0.80 torr). IR: 2976, 2874,

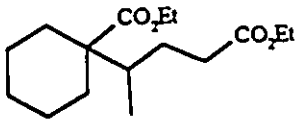
1738, 1726, 1453, 1371, 1178, 1029 cm^{-1}; ^1H NMR: 4.06 (m, 4H), 2.21 (t, 2H, J=7.1), 2.08-1.43 (m, 12H), 1.19 (t, J=7.1, 6H); ^{13}C NMR: 177.6, 173.4, 60.33, 60.26, 53.9, 38.6, 36.1, 34.7, 25.0, 21.5, 14.3; MS: m/z 256, (M+); HRMS: calculated for $C_{14}H_{24}O_4$ 256.1675 (M+), found 256.1679.

Ethyl (*E*)-4-(1-ethoxycarbonyl-2-methylcyclohexyl)-2-butanoate (**118**)



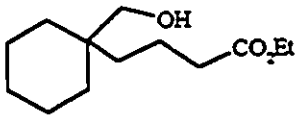
Subjecting compound **110** (0.331 g, 1.17 mmol) to procedure (IV) produced compound **118** (0.290 g, 87%), which was purified by bulb to bulb distillation (85 °C/0.3 torr). Compound **118** was identified spectroscopically, IR: 2933, 2863, 1735, 1463, 1449, 1374, 1177, 1156, 1096, 1029, 917, 734 cm^{-1}; ^1H NMR: δ 4.10 (q, 2H, J=7.1), 4.10 (q, 2H, J=7.1), 2.26-1.30 (m, 15H), 0.92 (t, 6H, J=7.1), major 0.92 (d, 3H, J=7.0), minor 0.81(d, 3H, J=7.1); ^{13}C NMR: δ major 176.6, 173.5, 60.3, 59.9, 49.2, 37.4, 35.7, 35.0, 34.8, 29.6, 27.8, 22.5, 22.0, 20.0, 16.5, 14.4, minor 49.6, 30.4, 30.3, 29.8, 23.2, 22.2, 19.8, 15.6; MS: m/z 284; HRMS: calculated for $C_{16}H_{28}O_4$ 284.1988 (M+), found 284.1993.

Ethyl 4-(1-ethoxycarbonylcyclohexyl)-4-methylbutanoate (**119**)



Compound **107** (0.250 g, 0.89 mmol) was hydrogenated using procedure (IV) to produce compound **119** (0.200 g, 80%). Purification was performed using bulb to bulb distillation (97 °C/0.50 torr). Compound **119** was identified spectroscopically, IR: 2977, 2934, 2859, 1735, 1725, 1450, 1384, 1198, 1177, 1129, 1028, 851cm^{-1}; ^{1}H NMR: δ 4.09 (q, 2H, J=7.0), 4.09 (q, 2H, J=7.0), 2.40-1.18 (m, 21H), 0.81 (d, 3H, J=6.8); ^{13}C NMR: δ 176.0, 173.8, 60.4, 60.0, 50.8, 41.1, 33.3, 31.6, 31.3, 26.9, 26.0, 23.74, 23.68, 14.5, 14.3, 13.9; MS: m/z 284 (M+); HRMS: calculated for $C_{16}H_{28}O_4$ 284.1988 (M+), found 284.1982.

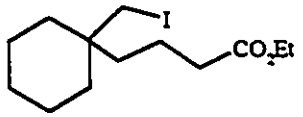
Ethyl 4-[(1-hydroxymethyl)cyclohexyl]butanoate (**130**)



Subjecting compound **112** (0.316 g, 1.41 mmol) to procedure (IV) afforded pure **130** (0.257 g, 80%) after bulb to bulb distillation (100 °C/1 torr). Compound **130** was identified spectroscopically, IR: 3447 (br), 2928, 2853, 1735, 1457, 1374. 1041, 861 cm^{-1}; ^{1}H NMR: δ 4.10 (q, 2H, J=7.1), 3.40 (s, 2H), 2.27 (t, 2H, 6.9), 2.10 (br, 1H), 1.54-1.20

(m, 17H); ^{13}C NMR: δ 174.3, 68.4, 60.5, 37.2, 34.6, 33.8, 32.6, 26.5, 21.6, 18.2, 14.3; HRMS: calculated for $C_{13}H_{24}O_3$ 228.1725 (M+), found 228.1717.

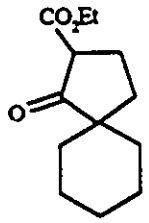
Ethyl 4-[(1-iodomethylcyclohexyl)butanoate (**131**)



Compound **130** (0.112 g, 0.50 mmol) was added to a flask containing triphenylphosphine (0.390 g, 1.49 mmol), imidazole (0.100 g, 1.49 mmol) , and iodine (0.250 g, 0.99 mmol). Toluene (25 mL) was added and the mixture was allowed to reflux for four hours. At this time the mixture was allowed to cool to room temperature, sodium bicarbonate was added, and stirring was allowed to continue for five minutes. Iodine was then added until the toluene layer remained orange. A saturated aqueous sodium thiosulphate solution was added to remove the excess iodine, at which time a conventional workup was performed by extracting with toluene. The crude product was purified by flash chromatography (2:1 petroleum ether: diethyl ether) to afford **131** (0.145 g, 87%) (bp 100 °C/0.48 torr). Compound **131** was identified spectroscopically, IR: 2927, 2855, 1735, 1454, 1372, 1258, 1169, 1035, 801 cm^{-1} ;^{1}H NMR: δ 4.10 (q, 2H, J=6.8), 3.20 (s, 2H), 2.27 (t, 2H, J=6.9), 1.52-1.20 (m, 17 H); ^{13}C NMR: δ 173.7, 60.4, 37.4, 35.2, 35.0, 34.8, 26.2, 21.9, 18.4, 14.4; MS: m/z 338 (M+); HRMS: calculated for $C_{13}H_{23}IO_2$ 338.0743 (M+), found 338.0732.

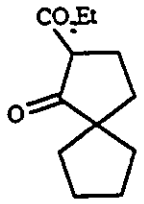
General Procedure for Dieckmann Condensation. Procedure V [53]

2-Ethoxycarbonyl-1-oxospiro[4.5]decane (**120**)



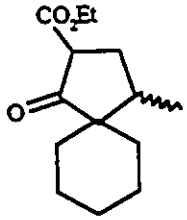
Potassium hydride (0.060 g, 1.58 mmol) was washed three times with dry diethyl ether under nitrogen. After the third washing, dry diethyl ether (20 mL) was added, followed by compound **117** (0.355 g, 1.31 mmol). The mixture was allowed to stir overnight. 3 M HCl was added and the mixture was stirred for an additional 5 minutes after which an aqueous workup was performed. The crude product was purified by bulb to bulb distillation (85 °C/0.20 torr) to afford compound **120** (0.247 g, 84%). Compound **120** was identified spectroscopically, IR: 2928, 2861, 1749, 1723, 1651, 1445, 1233, 891 cm^{-1}; ^{1}H NMR: 4.17 (q, 2H, J=7.1), 3.19 (t, 1H, J=9.0), 2.21-1.49 (m, 14H), 1.26 (t, 3H, J=7.1); ^{13}C NMR: 216.2, 169.9, 61.4, 57.1, 54.4, 37.3, 36.4, 26.0, 25.9, 24.4, 24.4, 14.3; MS: m/z 224 (M+); HRMS: calculated for $C_{13}H_{20}O_3$ 224.1412 (M+), found 224.1410.

2-Ethoxycarbonyl-1-oxospiro[4.4]nonane (**121**)



Subjecting compound **116** (0.178 g, 0.695 mmol) to procedure V produced compound **121** (0.101 g, 69%). The compound was purified by Kugelrohr distillation (83°C/0.29 torr). Compound **121** was identified spectroscopically, IR: 2955, 2867, 1749, 1723, 1655, 1447, 1249, 1195, 1128, 900 cm^{-1}; ^{1}H NMR: δ 4.16 (q, 2H, J=7.1), 3.18 (t, 1H, J=8.9), 2.20-1.44 (m, 12H), 1.25 (t, 3H, J=7.1); ^{13}C NMR: δ 216.2, 169.9, 61.3, 57.0, 54.4, 37.2, 36.4, 36.3, 26.0, 25.9, 24.4, 14.2; MS: m/z 210 ($M^{+\cdot}$); HRMS: calculated for $C_{13}H_{18}O_3$ 210.1256 (M+), found 210.1248.

2-Ethoxycarbonyl-1-oxo-4-methylspiro[4.5]decane (**122**)

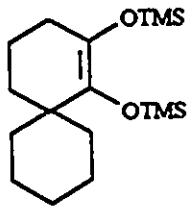


Subjecting compound **119** (0.048 g, 0.169 mmol) to procedure V produced compound **122** (0.020 g, 53%) as a 1:1 mixture of diastereomers. Purification was performed by bulb to bulb distillation (90 °C/0.68 torr) and preparative TLC (5:1

petroleum ether: ethyl acetate). Compound **122** was identified spectroscopically, IR: 2931, 2857, 1748, 1723, 1654, 1450, 1254, 1177, 800 cm^{-1}; ^{1}H NMR: δ 4.16 (q, 2H, J=7.1), diastereomer A 3.26 (t, 1H, J=9.2), diastereomer B 3.19 (t, 1H, J=9.4), 2.45-1.16 (m, 16H), diastereomer A 1.01 (d, 3H, J=6.8), diastereomer B 0.93 (d, 3H, J=7.1); ^{13}C NMR: δ 215.3, 214.9, 170.0, 170.0, 61.4, 54.0, 52.3, 51.3, 39.8, 36.3, 32.6, 32.3, 31.9, 31.0, 29.8, 27.5, 26.0, 25.9, 25.7, 25.4, 22.0, 21.8, 21.1, 16.1, 15.4, 14.7, 14.3, 14.1: MS: m/z 238 (M+); HRMS: calculated for $C_{14}H_{22}O_3$ 238.1569 (M+), found 238.1570.

General Procedure for the Acyloin Condensation. Procedure (VI)[40]

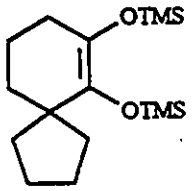
Bis (1,2-trimethylsiloxy)spiro[5.5]undec-1-ene **(123)**



Sodium metal (0.683 g, 0.333 mmol) and potassium metal (0.030 g, 0.683 mmol) were placed in a two neck flask under argon and washed with dry diethyl ether three times. The metal alloy was formed by heating the flask with a heat gun and constant stirring. After formation, the alloy was allowed to cool and diethyl ether (40mL) was added. Compound **117** (0.090 g, 0.333 mmol) and TMSCl (0.150 g, 1.37 mmol) were added simultaneously over 40 minutes using a syringe pump. The solution turned a purple

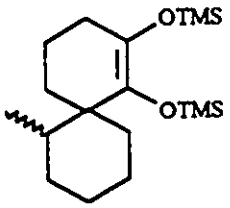
colour during this time. The mixture was allowed to stir overnight, at which time it was filtered through Celite ® under nitrogen. The solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography (10:1 petroleum.ether: diethyl ether) to produce a clear, colourless liquid, **122** (0.092 g, 85%). Compound **123** was identified spectroscopically, IR: 2929, 2860, 1676, 1292, 1250, 1207, 843, 758 cm^{-1} ^1H NMR: δ 2.10-0.85 (m, 16H), 0.17 (s, 18H); ^{13}C NMR: δ 139.5, 131.9, 38.3, 33.8, 31.1, 30.3, 26.2, 21.9, 19.0, 1.5, 1.2; MS: m/z 326 (M+); HRMS: calculated for $C_{17}H_{34}O_2Si_2$ 326.2097 (M+), found 326.2109.

Preparation of Bis (1,2-trimethylsiloxy) spiro[4,5] dec-1-ene **(123)**



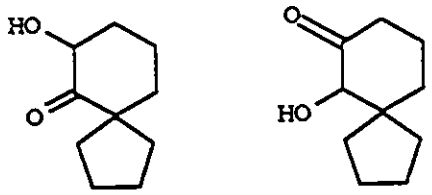
Subjecting compound **116** (0.460 g, 1.80 mmol) to procedure VI produced the pure spirocycle (0.262g, 47%) after flash chromatography (10:1 petroleum ether:diethyl ether). Compound **123** was identified spectroscopically, IR: 2954, 2863, 1677, 1444, 1250, 842, 757cm^{-1}; ^1H NMR: δ 2.11-1.23 (m, 14H), 0.17 (s, 9H),0.15 (s, 9H); ^{13}C NMR: 137.4, 131.3, 46.6, 37.2, 36.8, 30.2, 25.6, 20.5, 1.55, 1.16; MS: m/z 312 (M+); HRMS: calculated for $C_{16}H_{32}O_2Si_2$ 312.1941 (M+), found 312.1941.

Bis(1,2-trimethylsiloxy)-7-methylspiro[5.5]undec-1-ene (**124, 125**)



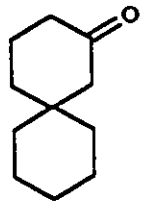
Compound **118** (0.088 g, .310 mmol) was subjected to procedure VI. The crude product was purified by flash chromatography (10:1 petroleum ether:diethyl ether) to provide a mixture of diastereomers (4:1) (0.045 g, 43%) (**124, 125**), and the major diastoereomer could be separated by preparative TLC (petroleum ether) to provide compound **124** . Compounds **124** and **125** were identified spectroscopically, IR: 2955, 2930, 2862, 1668, 1250, 1207, 843, 758 cm^{-1}; ^{1}H NMR: δ 0.15 (s, 9H), 0.17 (s, 9H), minor 0.71 (d, 3H, J=6.8) major 0.96 (d, 3H, J=6.5), 1.13-2.15 (m, 15H); ^{13}C NMR: δ major 139.8, 131.7, 40.4, 37.5, 35.2, 33.9, 30.3, 30.0, 22.3, 22.0, 18.5, 17.1, 1.72; minor 138.35, 132.5, 42.0, 35.8, 33.7, 30.4, 30.0, 18.8, 17.3, 1.35; MS:m/z 340 (M+); HRMS: calculated for $C_{18}H_{36}O_2Si_2$ 340.2254 (M+), found 340.2261.

2-Hydroxy-1-oxospiro[4.5] decane and 1-hydroxy-2-oxospiro[4.5]decane (**126, 127**)



Compound **123** (0.241 g, 0.78mmol) was added to a round bottom flask followed by acetone (15mL). Five drops of concentrated HCl were added, and the mixture was allowed to stir for one half hour. The mixture was subjected to a conventional workup and was purified by flash chromatography (5:1 petroleum ether:ethyl acetate) to provide compounds **126** and **127** (0.030 g, 23%) as a 2:1 regioisomeric mixture. Compounds **126** and **127** were identified spectroscopically, IR: 3481 (br), 2946, 2867, 1712, 1105 cm^{-1}; ^{1}H NMR: δ minor 4.28 (d of d, 1H, J=6.7, J=12.3), major 4.06 (s, 1H), minor 3.70 (br, 1H), major 3.58 (br, 1H), 2.48-0.86 (m, 14H); ^{13}C NMR: δ 215.4, 211.5, 80.9, 73.0, 56.1, 53.1, 40.2, 39.0, 38.5, 36.8, 36.6, 36.2, 34.0, 28.6, 26.9, 25.5, 25.5, 24.7, 23.4, 20.4; MS: m/z 168 (M+); HRMS: calculated for $C_{10}H_{16}O_2$ 168.1150 (M+), found 168.1158.

2-Oxospiro[5.5]undecane (132)



t-BuLi (1.03 mmol) was added to a two neck flask containing of dry diethyl ether (20 ml) at -100 °C. Compound **131** was added (0.174 g, 5.15 mmol) and the mixture was allowed to warm to -50 °C . At this time the reaction was quenched with $NaHCO_{3(sat)}$ and a conventional workup was performed. The product was separated by flash chromatography (5:1 petroleum ether: ethyl acetate) to produce **132** (0.020 g, 24%). Compound **132** was spectroscopically identical with previously published results.[55]

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