MICHAEL-TERMINATED TANDEM REACTIONS FOR THE SYNTHESIS OF NITROGEN AND SULFUR HETEROCYCLES AND SUBSTITUTED SPIRANES

By

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PREFACE

A tandem S_N2-Michael addition sequence has been developed for the preparation of 5- and 6-ring nitrogen and sulfur heterocycles from ethyl ω-halo-2-alkenoates. The preparation of nitrogen heterocycles involves reaction of the haloester with a primary amine and triethylamine in methanol or ethanol solvent. This initially affords a secondary amine intermediate which then cyclizes onto the acrylate acceptor to form the heterocyclic product. The formation of sulfur heterocycles involves reaction of the haloester with thiourea to initally yield the isothiuronium halide adduct which is then hydrolyzed in aqueous base to afford the sulfur heterocyclic product proceeding through a thiolate intermediate. The process is useful for the preparation of mono-, fused- and spirocyclic rings having an acetate residue at C-2 relative to the heteroatom. The reactions proceed in 60-80% yields and can be carried out in a single reaction flask. The mechanism, stereochemistry, and scope of these reactions are discussed.

A one-pot tandem decarboxylation-Michael addition sequence has also been developed for the construction of functionalized spiranes. Starting substrates were readily prepared by alkylation of methyl 2-oxocycloalkanecarboxylates with a side chain group incorporating a terminal acrylate Michael acceptor. The process is initiated by nucleophilic ester cleavage-decarboxylation of the cyclic β-ketoester with lithium chloride in hexamethylphosphoramide (HMPA) solvent at 95-130°C and the resulting anion is trapped by subsequent Michael addition to the side-chain acrylate acceptor. Both 5- and 6-rings can be prepared by this procedure. Yields range from 50-70% and closure occurs such that the two carbonyl groups are oriented trans to one another in the major product.

ACKNOWLEDGEMENTS

I wish to express sincere appreciation to my research advisor, Dr. Richard A. Bunce, whose patient guidance, sound advice and genuine enthusiasm has made the completion of this work possible. Appreciation is also extended to my committee members, Dr. Elizabeth M. Holt, Dr. K. Darrell Berlin, Dr. Horatio A. Mottola and Dr. Richard C. Essenberg. An additional amount of graditude is extended to Dr. Holt for her crystallographic assistance throughout the course of this work and also for her sound advice and helpful insights during my graduate career here. Gratitude is extended also to Dr. K. Darrell Berlin for his helpful discussions regarding N.M.R. experiments and their interpretation and to Dr. Christopher M. Adams for the use of his HPLC equipment. Special thanks are in order for Stan Sigle, Paul West, and Jeff Archer for their technical assistance. I am especially grateful to those members of the research group, both past and present, especially Dr. Vicki L. Taylor, Kelly Sprankle and Derek Irwin, whose support and friendship have made this work enjoyable. Gratitude is extended also to several current graduate students of this department, most notably John Schemenaur, Allen Engle, and Mike Cagle, whose advice, friendship, stimulating discussions and personal insights have made these graduate years enjoyable, informative and interesting.

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I gratefully acknowledge the Oklahoma Center for the Advancement of Science and Technology (Nos. HR8-084 and HR1-035) and DowElanco who have provided the financial support for this work.

Finally, I wish to dedicate this thesis to my family, my parents Richard and Francis Peeples, and my sisters, Suzanne and Jennifer Peeples. Their unconditional love, unending moral support and ceaseless encouragement were essential in attaining this goal.

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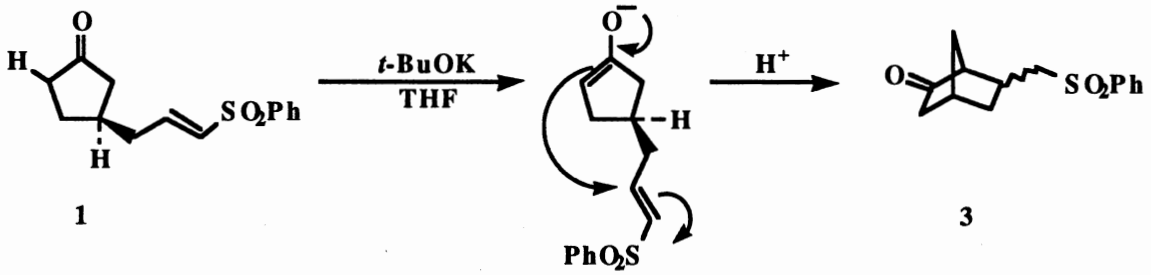
HISTORICAL BACKGROUND: THE UTILITY OF THE MICHAEL ADDITION IN TANDEM REACTION PROCESSES

Introduction

This chapter presents a brief overview of the use of the Michael addition in tandem reaction sequences. Attention has been focused on several strategies that have been devised involving the integration of the Michael addition reaction into tandem sequences that allow for the efficient preparation of a number of different types of organic compounds having both synthetic and practical utility. Specific examples have been included to illustrate these applications.

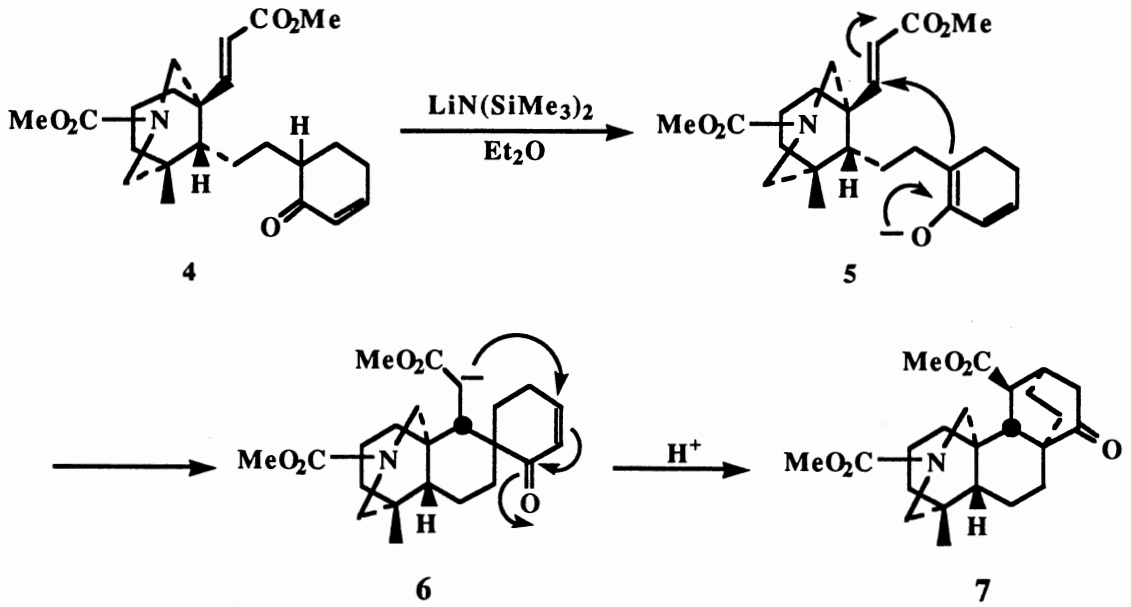
Preparation of Carbocyclic Compounds

The Michael addition has been utilized extensively as a component step in tandem reaction sequences for the preparation of many useful carbocyclic systems.[1-26] One of the advantages of the use of the Michael reaction in such sequences is that one is able to efficiently construct ring systems of moderate to high structural complexity bearing useful functionality. For example, in an intramolecular Michael addition reported by Haynes and Katsifis,[1] treatment of the allyl phenyl sulfone **1** with potassium *tert*-butoxide in tetrahydrofuran cleanly afforded the bicyclo[2.2.1]heptanone derivative **3** (65%) proceeding through the intermediate enolate **2**.



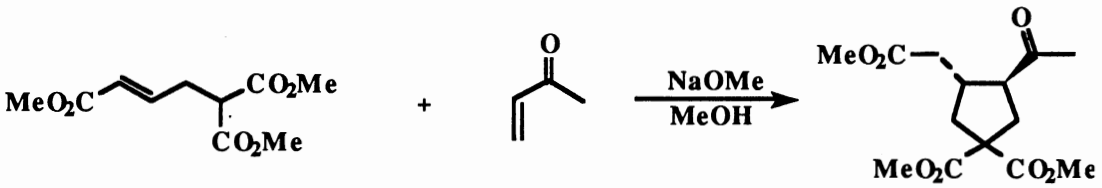
1 2 3

In a total synthesis of atisine, a diterpene alkaloid, Kametani and co-workers[2,3] utilized a tandem intramolecular Michael-Michael reaction to prepare the pentacyclic intermediate **7** from precursor **4**. Reaction of **4** with lithium bis(trimethylsilyl)amide in ether at -78°C smoothly generated kinetic enolate **5** which cyclized intramolecularly onto the methoxycarbonylethenyl moiety in Michael fashion to afford intermediate enolate **6**. Subsequent Michael addition of the ester enolate portion of **6** to the cyclohexenone functionality then yielded **7** in an overall yield of 58% following workup.

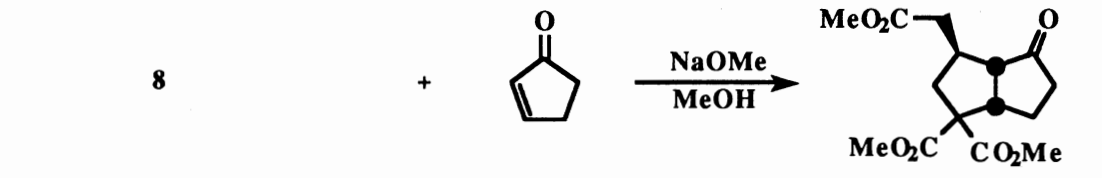


4 5 6 7

In a method involving a tandem intermolecular Michael addition-Michael addition sequence for the preparation of functionalized 1- and 2-ring carbocycles, Bunce and co-workers[4] utilized triester precursor **8** incorporating both a Michael donor and a Michael acceptor grouping. Reaction of **8** with an α,β-unsaturated ketone (**9** or **11**) in the presence of sodium methoxide generated products **10** and **12**. The reaction involves conjugate addition of the deprotoned malonate portion of **8** to ketone **9** (or **11**) to afford a carbanion intermediate which then undergoes an intramolecular Michael addition to the acceptor portion of **8** to yield the observed product (**10** or **12**) after workup. The method was found to be highly selective (up to *ca.* 50:1) for the preparation of the thermodynamic trans product.



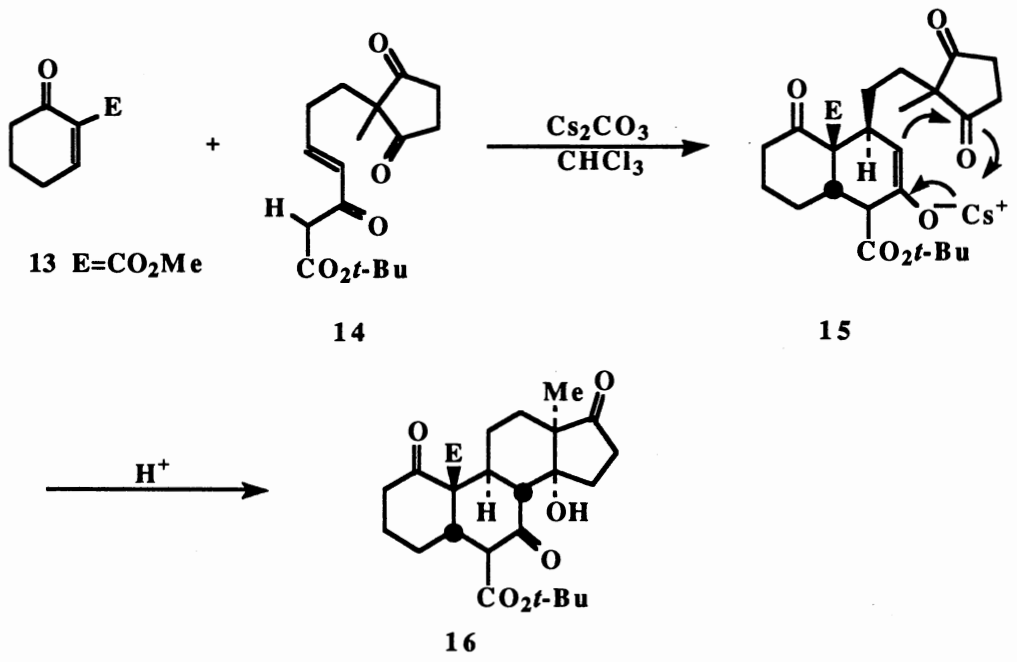
8 **9** **10**



11 **12**

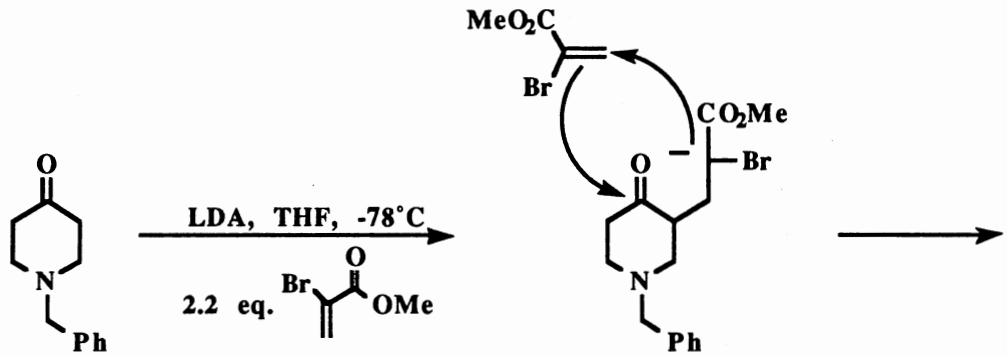
In efforts relating to the preparation of 13α-methyl 14α-hydroxy steroid derivatives, Lavallee and Deslongchamps[5] reported a preparation of tetracyclic intermediate **16** which involved a tandem Michael-Michael-aldol reaction. The reaction of **13** and **14** in

the presence of cesium carbonate in chloroform initially yielded intermediate **15** resulting from the Michael addition of the carbanion of **14** to **13**. This was followed by a second intramolecular Michael addition of the resulting β-ketoester carbanion moiety of **13** to the α,β-unsaturated ketone portion of **14**. Subsequent intramolecular aldol addition of the resulting enolate (**15**) to one of the two ketone functionalities of the neighboring 1,3-cyclopentanedione ring system smoothly afforded the observed product **16**.

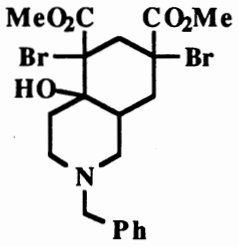


An example of an intermolecular Michael-Michael-aldol reaction sequence involving a very efficient and general, 2+2+2 synthesis of poly-functionalized cyclohexanols (**19**) was reported by Posner and co-workers.[6] The approach entailed reaction of piperidone **17** with 2.2 equivalents of methyl α-bromoacrylate and 1.0 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C. The reaction proceeds along a

pathway involving two sequential Michael additions and an aldol reaction as shown in **18** to afford cyclohexanol **19** (66% overall yield) after workup and purification.

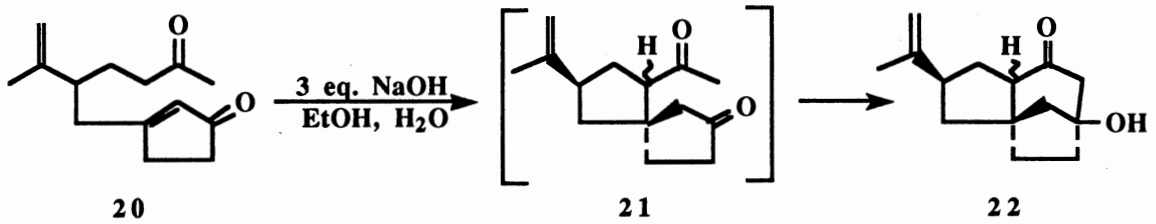


17 **18**

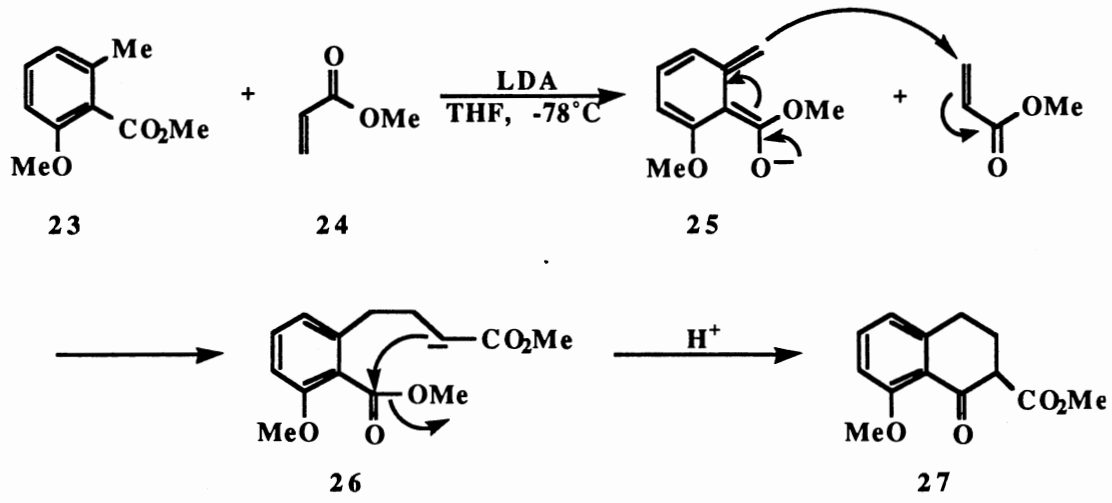


19

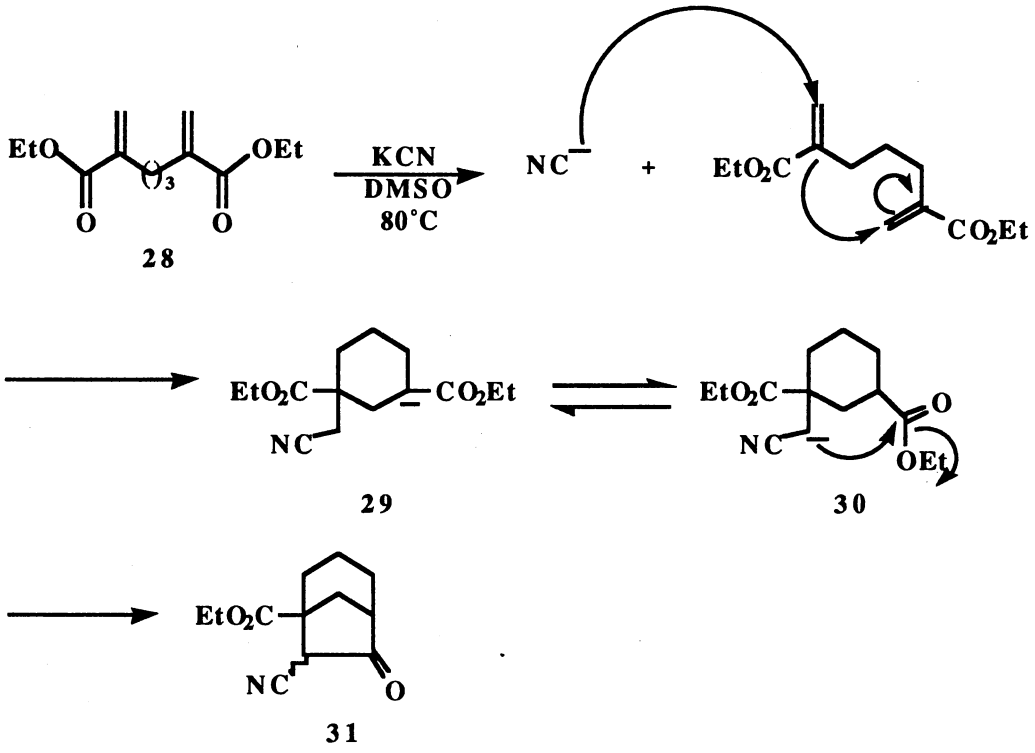
In an approach to the preparation of the bicyclo[3.2.1]octane ring system, a basic structural unit in a number of natural products, Alexakis and co-workers[7] utilized a tandem Michael-aldol route to prepare tricyclic product **22**. Reaction of **20** with sodium hydroxide afforded Michael addition product **21** which subsequently underwent an intramolecular aldol addition to yield **22**.



In a facile one-flask preparation of 8-methoxy-1-tetralones (**27**), Tarnachompoo and co-workers[8] described an efficient tandem Michael addition-Dieckmann condensation route involving the reaction of the methoxy toluate **23** and methyl acrylate (**24**). Reaction of **23** with lithium diisopropylamide in tetrahydrofuran at -78°C in the presence of **24** initially generated enolate **25** which then underwent Michael addition to **24** to afford intermediate **26**. Subsequent intramolecular Dieckmann condensation of **26** then yielded the enolate of **27** which was protonated on workup to afford the tetralone product in 52% yield.

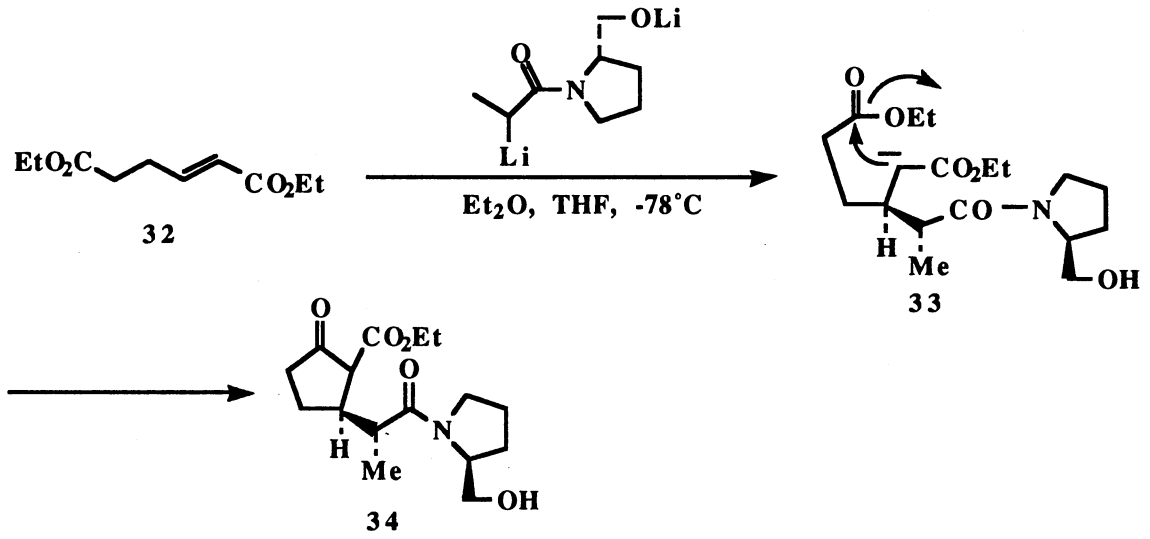


In another example illustrating a tandem Michael-Dieckmann approach to carbocycles, Stetter and co-workers[9] reported a method for the synthesis of bicyclo-[3.2.1]octane derivative **31** from diester **28**. Reaction of **28** with cyanide ion in dimethylsulfoxide at 80°C initially yielded enolate **29** resulting from the Michael addition of cyanide to one of the acrylate moieties. This was followed by intramolecular Michael addition, enolate equilibration (**29**→**30**) and Dieckmann condensation to afford **31** in an overall yield of 56% from **28**.

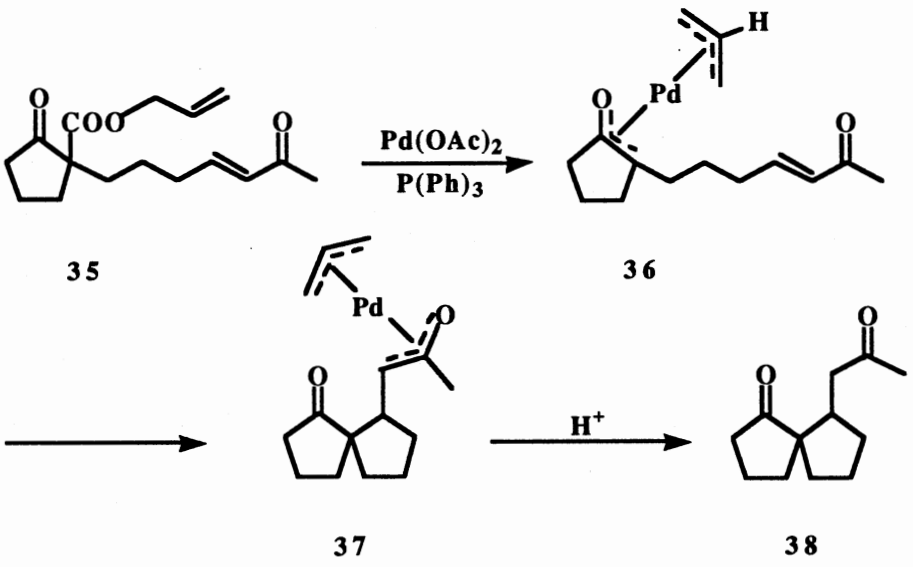


Yamaguchi and co-workers[10] illustrated the use of chiral reagents for the stereocontrolled construction of tertiary carbon centers using a tandem Michael-Dieckmann

scheme. Reaction of the dilithium derivative of (S)-(+)-*N*-methyl-*N*-propionylvalinol with diester **32** in ether-tetrahydrofuran at -78°C afforded chiral intermediate **33** by an intermolecular enantioselective Michael addition to the ene diester which subsequently cyclized through a Dieckmann condensation to give chiral **34** in 71% yield. The authors then proceeded to use **34** in a total synthesis of (+)-dehydroiridodiol.[11]

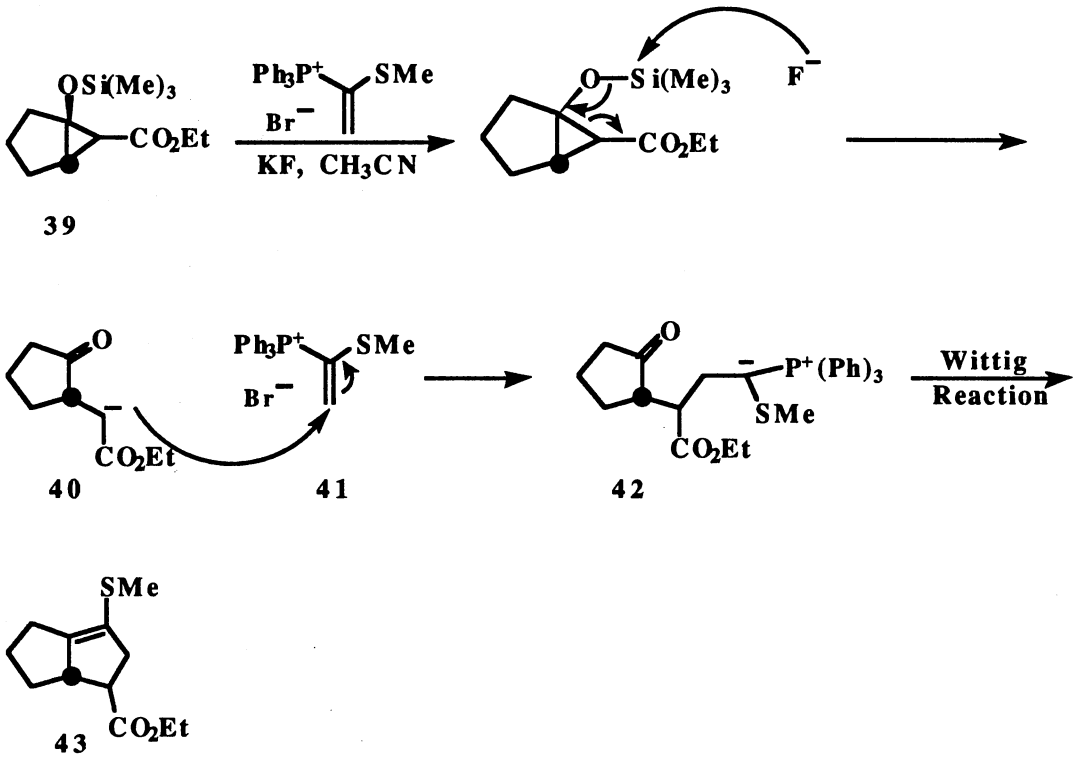


Another sequence utilizing the Michael addition in a tandem reaction scheme was reported by Nokami and co-workers.[12] In this work, the reaction of 2-allyloxycarbonyl-cyclopentanone **35** with palladium(II) acetate in the presence of triphenylphosphine in acetonitrile at 40°C initially generated the (π-allyl) palladium enolate **36** through decarboxylation of **35**. Subsequent formation of the (π-allyl) palladium enolate **37** from **36** through an intramolecular 1,4-addition of the palladium enolate moiety of **36** to the terminal enone functionality (and hydrolytic workup) smoothly afforded spiro adduct **38** in an overall yield of 69% from **35**.

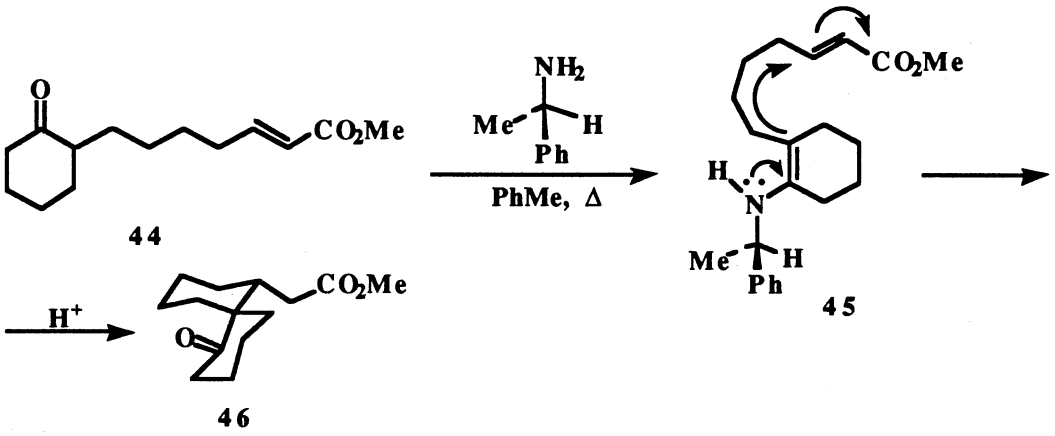


35 36 37 38

In a scheme devised for the preparation of functionalized diquinanes utilizing a [3+2] annulation route, Marino and co-workers[13] reported a process involving a tandem desilylation-Michael addition-Wittig reaction sequence that allowed for the facile preparation of diquinane **43** from cyclopropane **39**. Reaction of 2-(silyloxy)cyclopropane ester **39** with potassium fluoride in refluxing acetonitrile in the presence of 1-thiovinyl-phosphonium bromide (**41**) initially afforded γ-oxo ester enolate **40** through a fluoride-induced desilylation-cyclopropyl ring-opening sequence. Subsequent Michael addition of **40** to **41** yielded ylide **42** which then underwent an intramolecular Wittig olefination to afford the diquinane product **43** in an overall yield of 80%. In the same citation, the authors also illustrated the preparation of a series of functionalized triquinanes using this [3+2] annulation sequence.

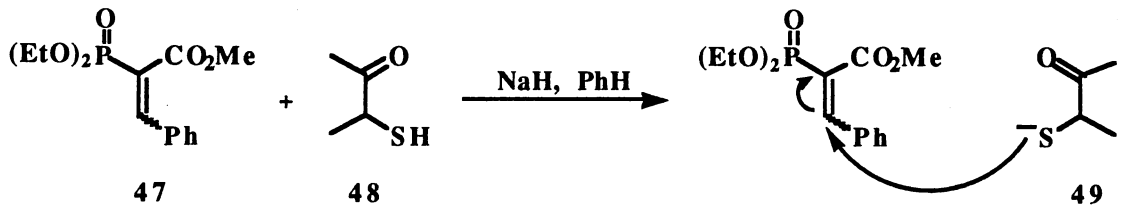


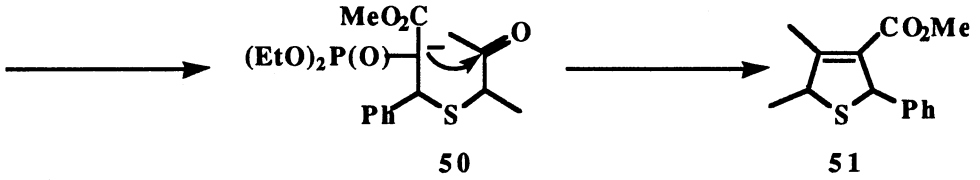
Lastly, d'Angelo and coworkers[14] described a route for an efficient asymmetric synthesis of spirane **46** from 2-substituted cyclohexanes (**44**) proceeding through a tandem imine formation-Michael addition sequence. Reaction of **44** with (R)-1-phenyl-ethylamine in refluxing toluene intially yielded the chiral imine. This species, which is in equilibrium with the thermodynamic enamine **45**, underwent an intramolecular Michael addition to the terminal enoate ester to afford spiro product **46** (85% conversion) following hydrolytic workup. According to the authors, this process allowed for the synthesis of **46** with a high level of stereochemical homogeneity as verified by ^{1}H-NMR and single crystal X-ray diffraction techniques.



Preparation of Heterocyclic Compounds

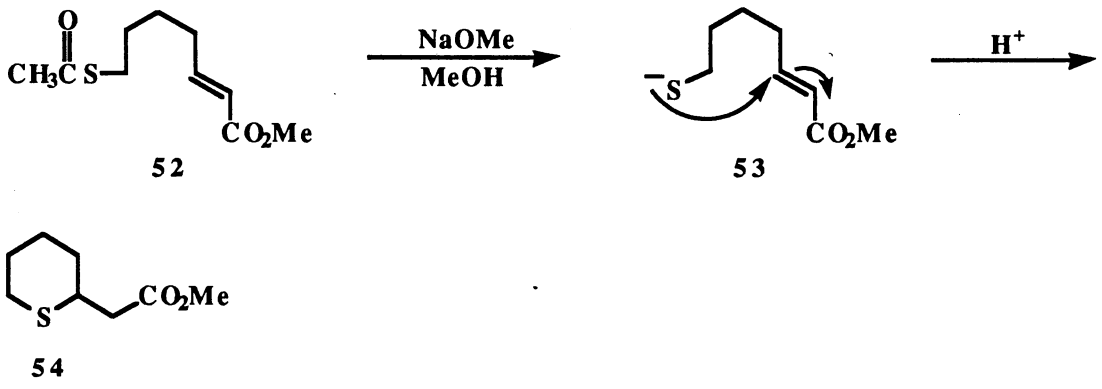
In 1975, McIntosh and co-workers[15,16] reported a procedure for the efficient preparation of 2,5-dihydrothiophenes (i.e. **51**) from α-mercaptoketone **48** and phosphonate **47**. Reaction of **48** with sodium hydride in the presence of **47** in benzene solvent initially yielded thiolate **49**. Subsequent Michael addition of **49** to **47** then afforded the phosphonate anion **50** which underwent an intramolecular Wadsworth-Emmons olefination to yield thioether **51** (72% overall conversion from **48**). The preparation of dihydrothiophenes has received much attention because of their facile conversion to substituted butadienes[17] through an oxidation-thermal decomposition route.





50 51

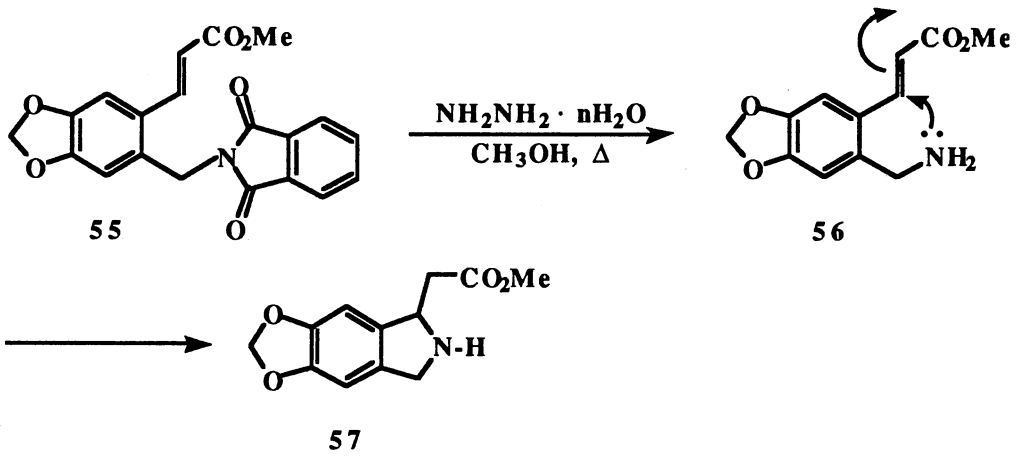
During the preparation of substrates for ring expansion studies of sulfur heterocycles, Vedejs and co-workers[18] described a facile synthesis of tetrahydrothiopyran derivative **54** from **52** involving a tandem thioacetate methanolysis-Michael addition reaction sequence. Reaction of thioacetate **52** with sodium methoxide in methanol at 23°C resulted in acetate cleavage to form thiolate **53** which subsequently underwent an intramolecular Michael addition to afford methyl 2*H*-tetrahydrothiopyran-2-acetate (**54**) in 93% yield.



52 53 54

As part of a total synthesis of lycorine, Boeckmann and co-workers[19] reported an efficient one-flask preparation of dihydroisoindole **57** from phthalimide derivative **55**.

Treatment of **55** with hydrazine in refluxing methanol solvent resulted in mild hydrazinolysis of **55** to afford primary amine **56** which subsequently underwent intramolecular Michael addition to the ortho acrylate moiety to give **57** in an overall yield of 70% from **55**.



55 56 57

CHAPTER II

A TANDEM S_N2-MICHAEL ADDITION ROUTE TO 5- AND 6-RING NITROGEN AND SULFUR HETEROCYCLES

Introduction

Heterocylic ring systems are an important structural component of many natural products[27-30] and compounds used as medicinal agents.[31-35] Consequently, this class of organic structures has and continues to receive much attention in contemporary organic research. Work by Boeckman and co-workers[19] has illustrated the use of a tandem Gabriel amine synthesis-Michael addition sequence for the preparation of the dihydroisoindole ring portion (**4**) of the natural product lycorine. This approach is shown in Figure 1. This process involved the mild hydrazinolysis of phthalimide derivative **2** to yield primary amine **3** which then cyclized by a Michael addition process to afford the dihydroisoindole product **4** in a yield of 70%. This product (**4**) proved to be a key intermediate in a total synthesis of the natural product lycorine and several related compounds.

In view of these results, it was thought that a similar approach involving a tandem S_N2-Michael addition sequence resulting from the reaction of ω-halo-2-alkenoates **5** with a primary amine could potentially be used to prepare 5- and 6-ring nitrogen heterocycles **6** bearing useful functionality at C-2 on the heterocyclic ring as shown in Figure 2. In this study, several topics were of interest: 1) the design and optimization of reaction conditions for the process, 2) the elucidation of ring size effects in the closure step, 3) the structural variations possible in the closure products, and 4) the stereochemical selectivity in substrates where a chiral center would be introduced in the ring closure.

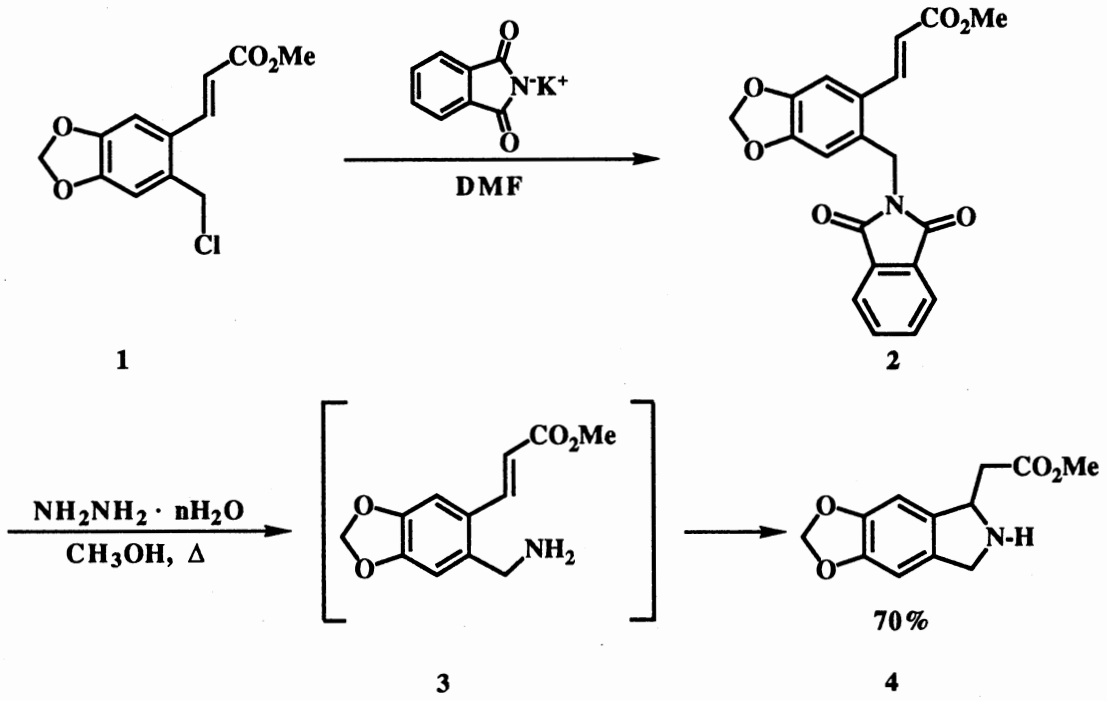


Figure 1. The Approach of Boeckman and Co-workers for the Preparation of Dihydroisoindole Derivative **4**.

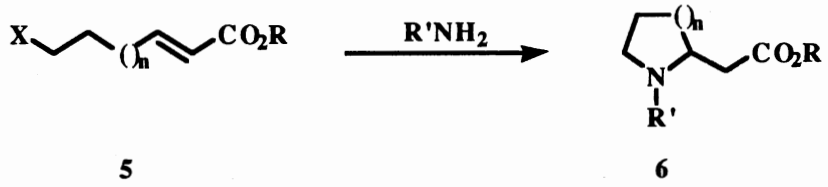
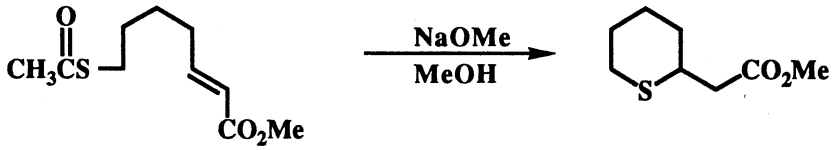


Figure 2. A Tandem S_N2-Michael Addition Approach for Preparing Nitrogen Heterocycles.

Previous work by Vedejs and co-workers[18] also demonstrated the use of a tandem thioacetate methanolysis-Michael addition sequence for the preparation of tetrahydro-thiopyran product **8** from thioacetate derivative **7** (see Figure 3). This method involved

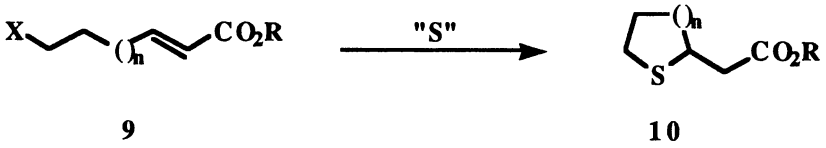
the treatment of **7** with methanolic sodium methoxide to yield the expected thiolate intermediate which then cyclized onto the acrylate moiety by a Michael addition process to afford product **8**.



7 **8**

Figure 3. The Method of Vedejs and Co-workers for the Preparation of Sulfur Product **8**.

In view of these observations, it was envisioned that a similiar approach involving a tandem S_N2-Michael addition sequence resulting from the reaction of haloester **9** with some organic or inorganic source of sulfur could be developed to prepare 5- and 6-ring sulfur heterocycles **10** bearing useful functionality (see Figure 4). In this portion of the



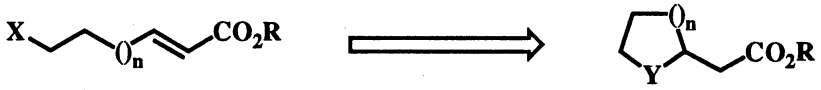
9 **10**

Figure 4. A Tandem S_N2-Michael Addition Approach for the Preparation of Sulfur Heterocycles.

study as well, several goals were set: 1) the determination of the best source of sulfur for the process, 2) the design of a set of optimized reaction conditions that would allow for the process to proceed smoothly, 3) the study of ring size effects in the closure step, 4) the structural variations possible in the closure products, and 5) the stereochemical selectivity in substrates where a chiral center would be introduced by such a process.

Results

Synthesis of the Starting Materials. A number of different starting substrates were prepared for use in our heterocyclization study. Compounds were selected for evaluation in the synthesis of simple, fused, and spiro ring systems. The synthesis of the starting substrates **11** for the preparation of a series of monocylic 5- and 6-ring nitrogen and sulfur heterocycles **12** (see Figure 5) is shown in Figure 6. Reaction of



11 n=1, 2

12 n=1, 2
Y=N-R', S

Figure 5. Preparation of Monocyclic Heterocycles **12** from Haloesters **11**.

tetrahydrofuran (**13**) and tetrahydropyran (**14**) with refluxing 48% hydrobromic acid[36] afforded 4-bromo-1-butanol (**15**) in 12% and 5-bromo-1-pentanol (**16**) in 15% yield respectively. Chloro alcohols **17** and **18** were available from commercial sources. Buffered oxidation of the 4- or 5-halo-1-alkanols **15-18** with pyridium chlorochromate[37]

to the corresponding halo aldehydes **19-22** followed by Wittig olefination using ethyl (triphenylphosphoranylidene)acetate in refluxing benzene smoothly afforded the ethyl (*E*)-6 or (*E*)-7-halo-2-alkenoates **23-26** in overall yields ranging from 52-57% (for **23** and **25**, respectively) from the starting halo alcohols **15** and **17**. Finally, treatment of **25** and **26** with sodium iodide in refluxing acetone cleanly afforded ethyl (*E*)-6-iodo-2-hexenoate (**27**) and ethyl (*E*)-7-iodo-2-heptenoate (**28**), respectively.

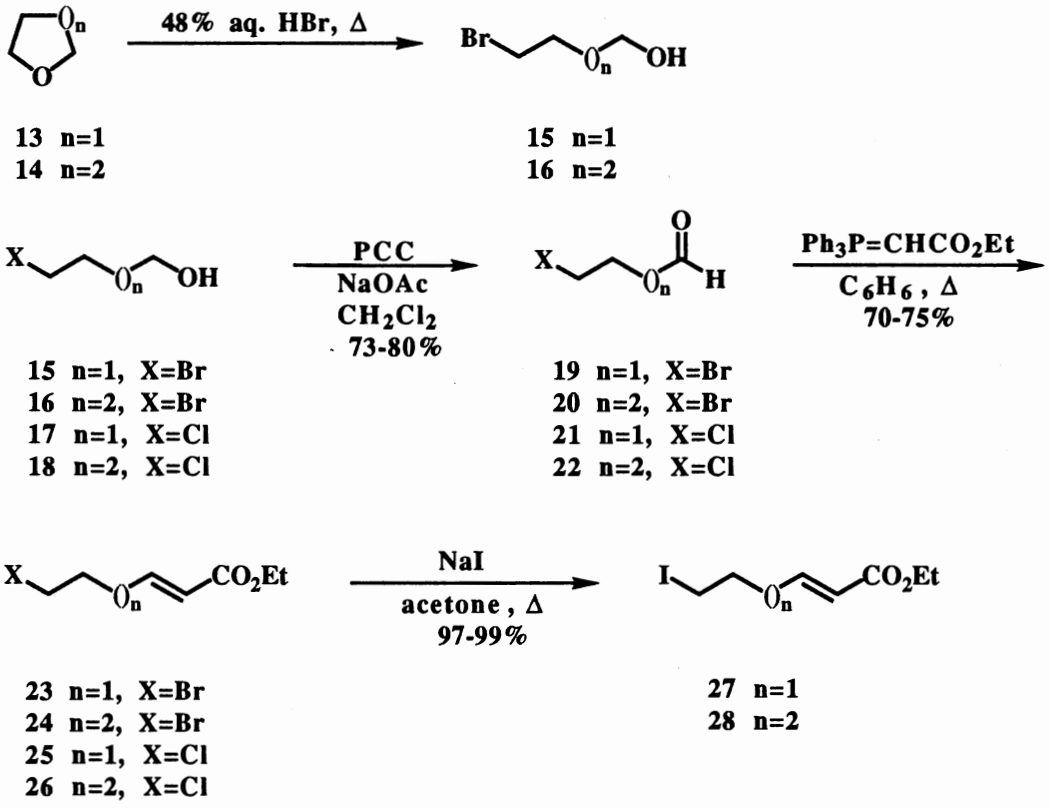
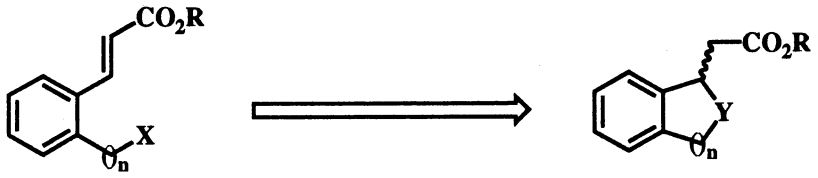


Figure 6. Synthesis of Haloester Precursors to Monocyclic Nitrogen and Sulfur Heterocycles.

The preparation of precursors **29** (see Figure 7) for the synthesis of several dihydroisoindoles (**30**, n=1, Y=N), tetrahydroisoquinolines (**30**, n=2, Y=N), 1,3-dihydrobenzo[*c*]thiophenes (**30**, n=1, Y=S), and 3,4-dihydro-1*H*-2-benzothiopyrans (**30**, n=2, Y=S) is shown in Figure 8. Wittig reaction of 2-methylbenzaldehyde (**31**)



29 n=1, 2

30 n=1, 2
Y=N-R', S

Figure 7. Preparation of Aromatic Nitrogen and Sulfur Heterocycles **30** from Haloesters **29**.

with methyl (triphenylphosphoranylidene)acetate, followed by benzylic bromination with *N*-bromosuccinimide[38] in carbon tetrachloride, smoothly afforded substrate **33** in an overall yield of 61%. The reaction of 2-phenylethanol (**34**) with paraformaldehyde and gaseous hydrochloric acid yielded isochroman[39] (**35**) which, upon sequential treatment with bromine and then 48% hydrobromic acid, afforded 2-(2-bromoethyl)benzaldehyde[39] (**36**) in an overall yield of 54% from **34**. Wittig olefination of **36** with ethyl (triphenyl-phosphoranylidene)acetate, followed by Finkelstein halide exchange with sodium iodide in acetone, yielded iodoester **38**.

The synthesis of substrate **39** allowing access to cis 6-5 fused-ring nitrogen and sulfur heterocycles **40** (see Figure 9) is illustrated Figure 10. Reduction of *cis*-1,2-cyclo-hexanedicarboxylic acid anhydride (**41**) with lithium aluminum hydride[40] in

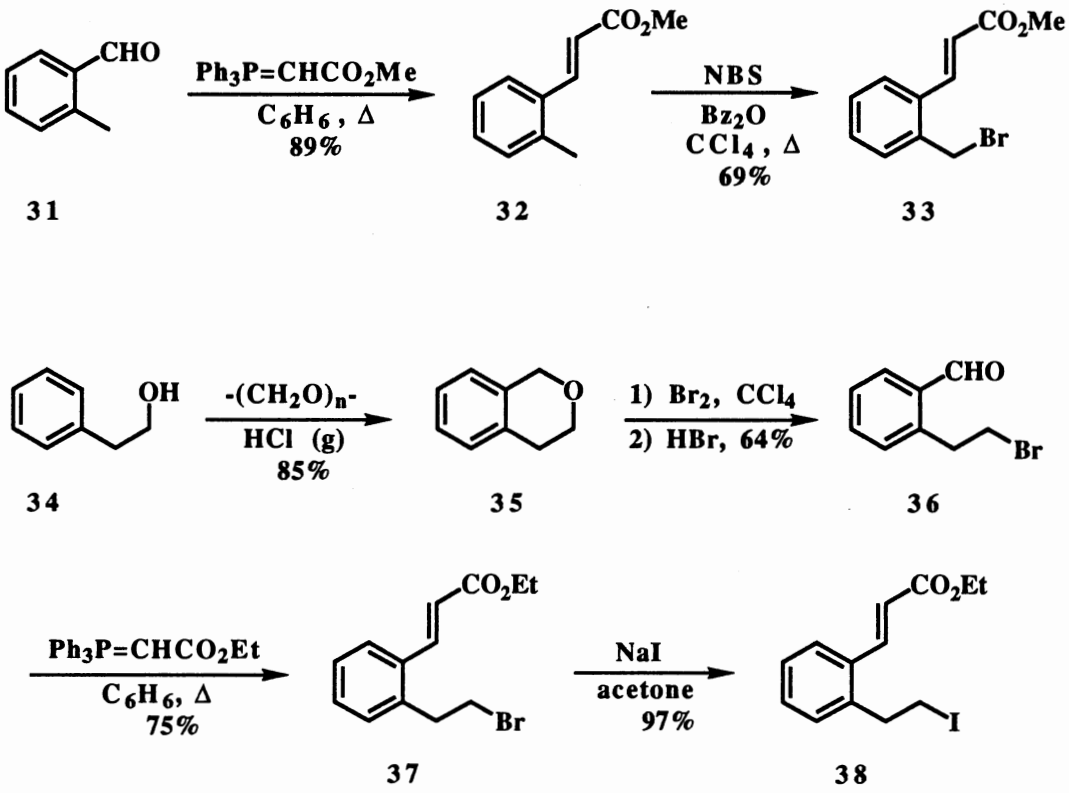


Figure 8. Synthesis of Starting Substrates **33** and **38**.

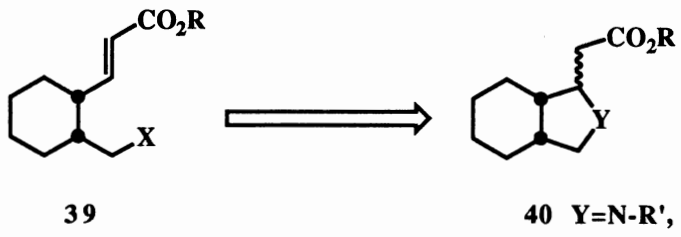


Figure 9. Preparation of cis 6-5 Fused-Ring Nitrogen and Sulfur Heterocycles **40** from Haloester **39**.

tetrahydrofuran, followed by oxidation of the cis diol intermediate **42** with manganese dioxide[41] in methylene chloride, afforded cis 6-5 fused-ring lactol product **43** in an overall yield of 81% from **41**. Wittig olefination of **43** with ethyl (triphenylphosphoranylidene)-acetate yielded hydroxyester **44**. Sequential treatment of **44** with methanesulfonyl chloride/triethylamine[42] in methylene chloride at 0°C and lithium bromide[43] in ether-HMPA afforded cis bromoester **46** in an overall yield of 90% from **44**.

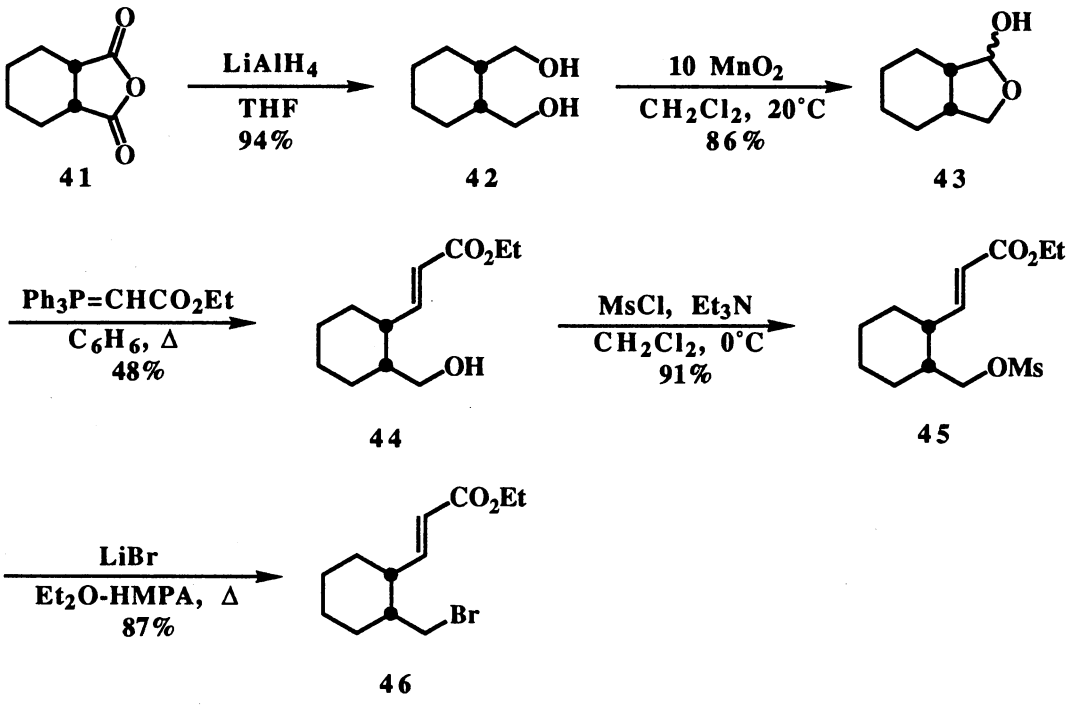
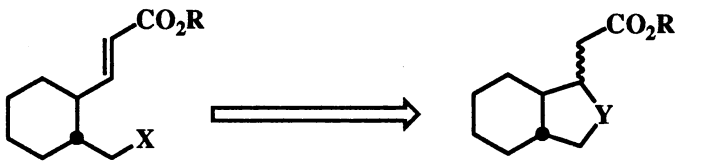


Figure 10. Synthesis of Substrate **46**.

The synthesis of substrate **47** allowing access to trans 6-5 fused-ring nitrogen and sulfur heterocycles **48** (see Figure 11) is illustrated in Figure 12. Reaction of **41** with ethanol and sulfuric acid[44] yielded cis diester product **49** in a yield of 90%. Base-induced

epimerization-hydrolysis[44] of **49** with ethanolic and then aqueous potassium hydroxide smoothly afforded the trans diacid **50** which was subsequently reduced with lithium aluminum hydride in tetrahydrofuran to yield *trans*-1,2-bis(hydroxymethyl)cyclohexane (**51**). The employment of the same reaction sequence described previously and shown in Figure 10 for the preparation of **46** from **42** allowed for the preparation of the trans bromoester **55** from **51** in an overall yield of 32%.



47 **48 Y=N-R', S**

Figure 11. Preparation of trans 6-5 Fused-Ring Nitrogen and Sulfur Heterocycles **48** from Haloester **47**.

The preparation of substrates **56** (see Figure 13) for the attempted syntheses of 3-substituted-2-(aza or thia)-spiro[4.4]nonanes (**57**, n=1, Y=N or S) and 3-substituted-2-(aza or thia)-spiro[4.5]decanes (**57**, n=2, Y=N or S) is illustrated in Figure 14. Fischer esterification[45] of cyclopentanecarboxylic acid (**58**) yielded ester **60** which was then alkylated with allyl bromide and lithium diisopropylamide[46] in tetrahydrofuran to afford **62**. Reduction of **62** with lithium aluminum hydride, followed by treatment of the alcohol intermediate **64** with triphenylphosphine in refluxing carbon tetrachloride,[47] yielded chloride **66** in an overall yield of 45% from **58**. Ozonolysis of **66**, followed by Wittig olefination with ethyl (triphenylphosphoranylidene)acetate in refluxing benzene,

afforded chloro ester **70**. The implementation of the same sequence of reactions allowed for the preparation of **71**, the 6-ring analog of **70**, from cyclohexane carboxylic acid (**59**).

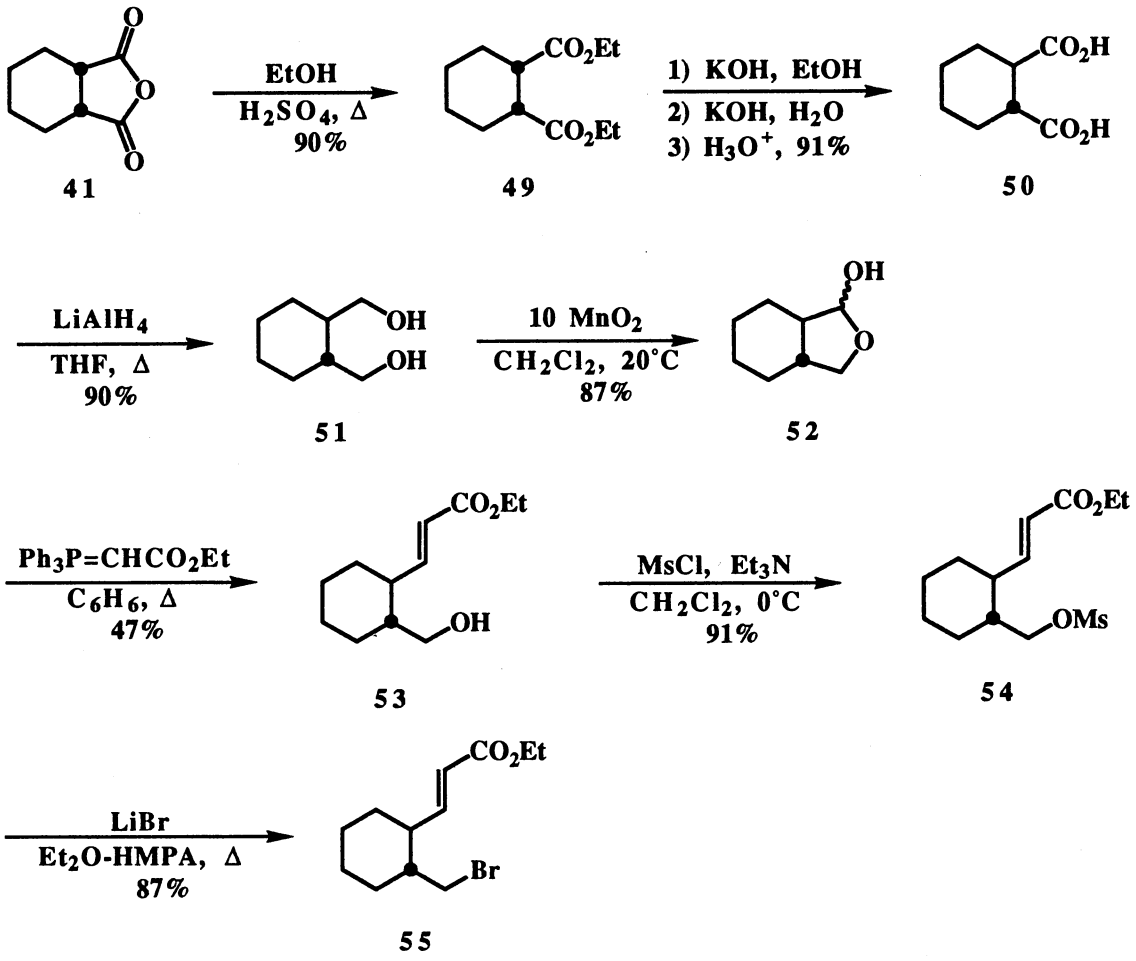


Figure 12. Synthesis of Substrate **55**.

Attempts to prepare the iodides of **70** and **71** using Finkelstein methodology, however, proved unsuccessful in both cases, probably due to the sterically-hindered nature of the chloromethyl moiety which inhibited approach of the iodide ion for displacement of the

chlorine atom. The corresponding bromide of **70** also exhibited a similiar lack of reactivity with regard to halogen exchange.[48]

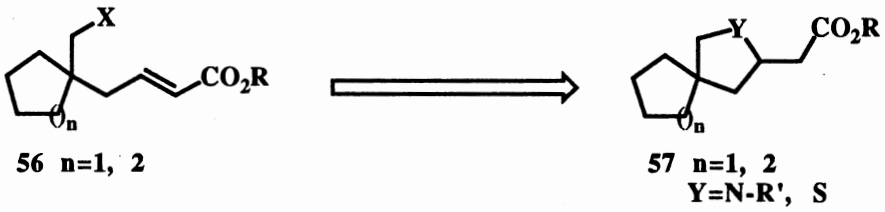


Figure 13. Preparation of Spiroheterocycles **57** from Haloesters **56**.

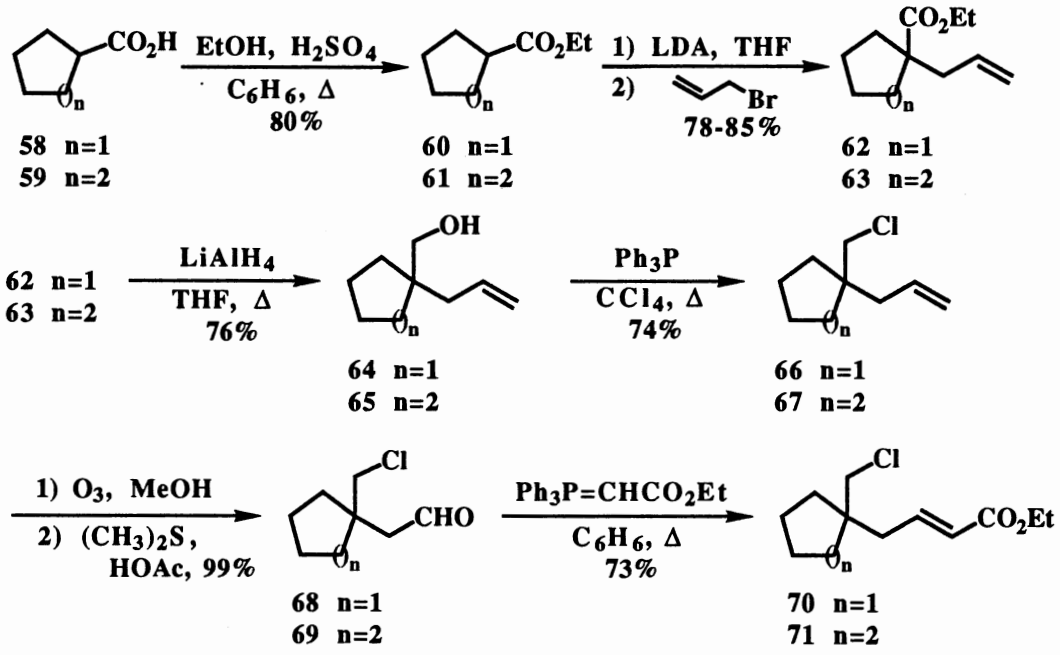
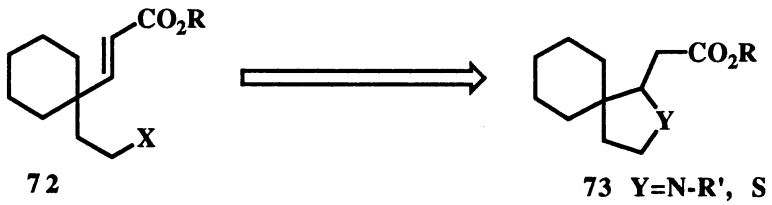


Figure 14. Synthesis of Substrates **70** and **71**.

Lastly, the synthesis of substrate **72** (see Figure 15) for the preparation of 2-substituted-3-azaspiro[4.5]decanes (**73**, Y=N) and 2-substituted-3-thiaspiro[4.5]decanes (**73**, Y=S) is illustrated in Figure 16. Reaction of cyclohexanone (**74**) with trimethyl phosphonoacetate and sodium hydride[49] in benzene afforded ethyl cyclopentylideneacetate (**75**) which was then reduced with lithium aluminum hydride[50] at 0°C to yield allylic alcohol **76** (79% overall yield from **74**). Treatment of **76** with triethyl orthoacetate containing a catalytic amount of propanoic acid at 140-145°C, followed by base hydrolysis, gave 1-vinylcyclohexaneacetic acid (**77**) in 72% yield. Reduction of **77** with lithium aluminum hydride, followed by mesylation[42] and treatment with LiBr[43], afforded bromide



72 **73 Y=N-R', S**

Figure 15. Preparation of Spiroheterocycles **73** from Haloester **72**.

80 in an overall yield of 63%. Ozonolysis of **80**, followed by Wittig olefination of the resulting aldehyde **81** with ethyl (triphenylphosphoranylidene)acetate in benzene, afforded bromoester **82** (70% overall yield from **80**).

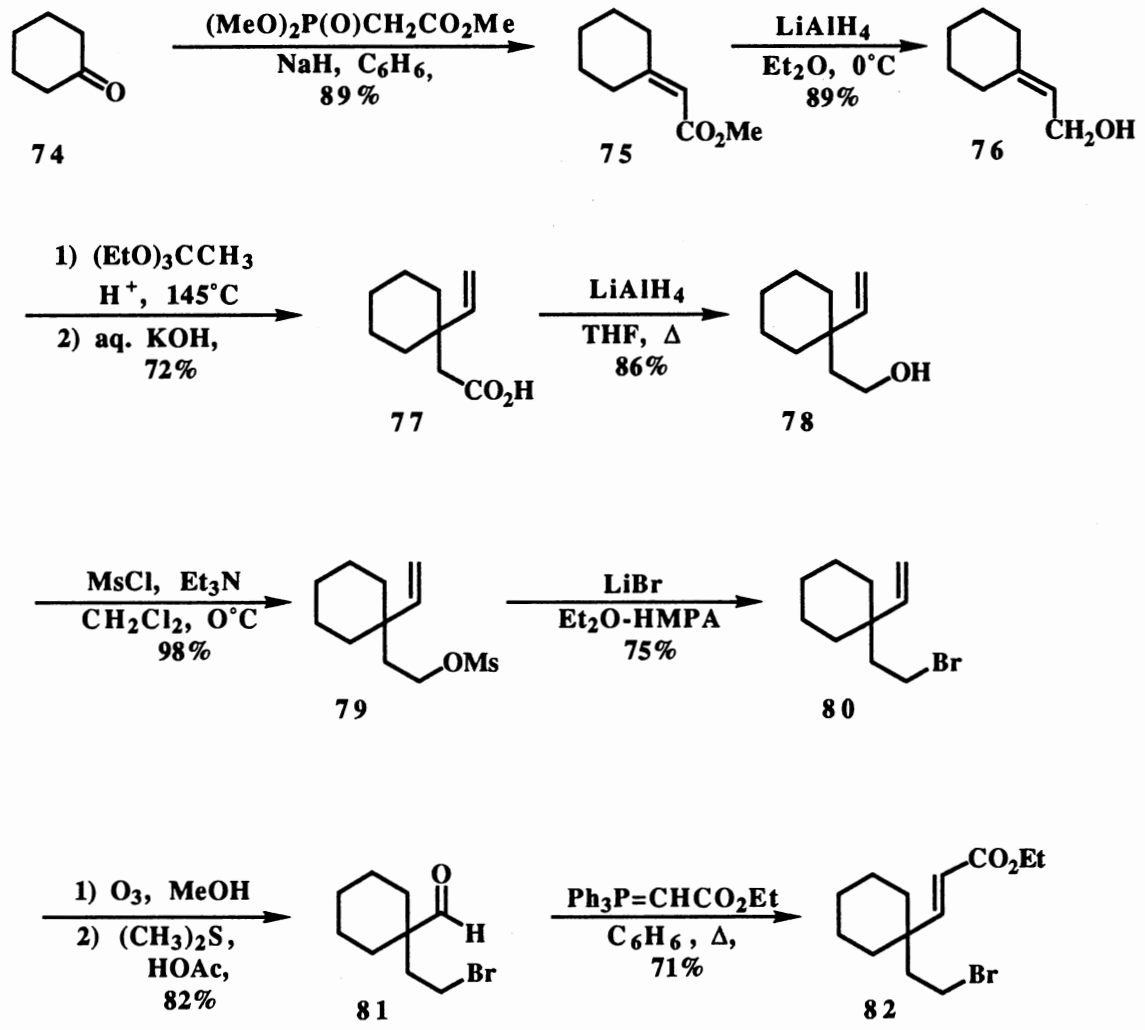


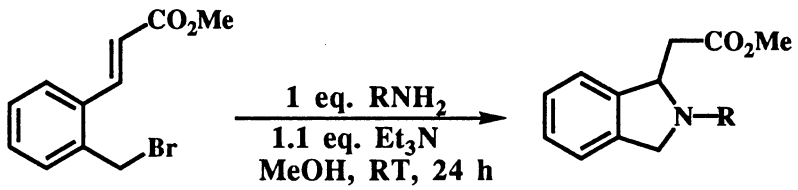
Figure 16. Synthesis of Starting Material **82**.

Preparation of 5- and 6-Ring Nitrogen Heterocycles. Our results on the use of the tandem S_N2-Michael addition sequence for the synthesis of nitrogen heterocycles are shown in Tables I and II. Reaction of the haloester with an equimolar amount of a primary amine in the presence of triethylamine in methanol or ethanol solvent afforded the 5- and 6-ring nitrogen heterocycles in yields ranging from 59-76% by a one-pot procedure. In the case of substrate **33**, the reaction conditions for formation of dihydroisoindole

products **83-85** did not require either heating or an extended reaction time as shown in Table I. This observation was probably due to both the enhanced reactivity of the benzylic bromide and the large degree of rigidity in substrate **33** which facilitated the ring closure by holding the nitrogen atom and the acrylate moiety in close proximity. Another interesting observation regarding the reactivity of **33** was that the reaction proceeded even when cyclohexylamine was used as the nitrogen donor although the observed yield was slightly lower. This presumably resulted from the increased steric hindrance surrounding the reacting amino group.

TABLE I

THE PREPARATION OF DIHYDROISOINDOLES BY A TANDEM S_N2-MICHAEL ADDITION REACTION SEQUENCE.



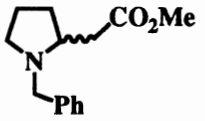
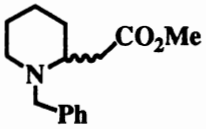
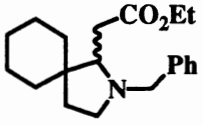
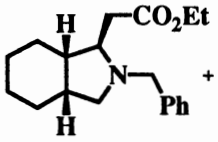
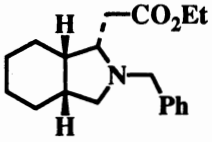
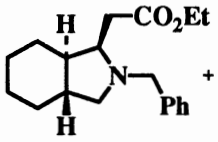
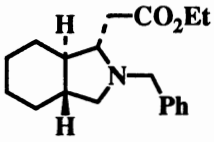
33 **83-85**

Product	R	% Yield[a]
83	$-CH_2CH_2Ph$	71
84	$-CH_2Ph$	69
85	$-c-C_6H_{11}$	62

[a]Yields refer to isolated, purified products

TABLE II

THE PREPARATION OF NITROGEN HETEROCYCLES BY A TANDEM S_N2-MICHAEL ADDITION SEQUENCE.

Starting Haloester	Product(s)	Yield[a]	Reaction Time[b]
27	 **86**	63%	Δ, 36 h
28	 **87**	59%	Δ, 36 h
82	 **88**	68%	Δ, 48 h
46	 +  **89** **90**	74%	Δ, 120 h
55	 +  **91** **92**	76%	Δ, 96 h

[a]Yields refer to isolated, purified products.
[b]All reactions were run using 1 eq of $PhCH_2NH_2$ and 1.1 eq Et_3N for the indicated time in MeOH or EtOH solvent.

As shown in Table II, the method can be used to prepare a number of monocyclic and bicyclic ring systems with the only difference in conditions being the required time of reaction. The reaction time required may reflect the relative amount of steric hindrance about the halomethyl portion of the substrate. The lack of reactivity shown by substrates **70** and **71** using this methodology is probably explained by the fact that the halides in each of these substrates are essentially neopentyl and, thus, inhibit the initial S_N2 reaction. The bromide analog of **70** also showed a similar lack of reactivity with a >80% recovery of starting material at the end of the heterocyclization attempt using the same conditions (see page 71) as cited for **70** and **71**.

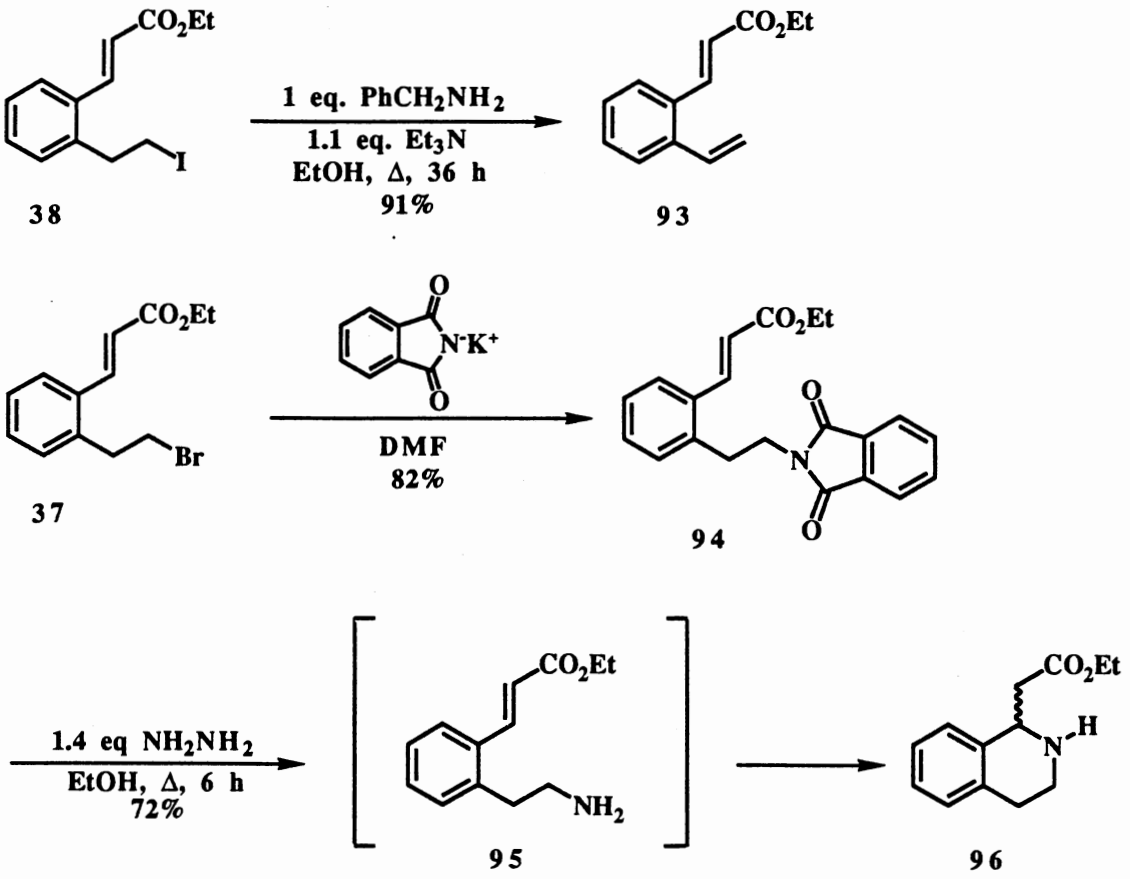


Figure 17. The Preparation of Tetrahydroisoquinoline **96**.

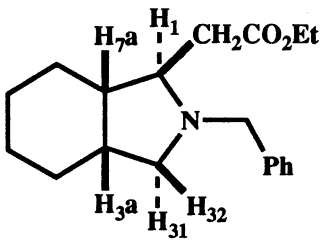
Application of this method to substrate **38** is shown in Figure 17. Reaction of iodoester **38** with benzylamine in the presence of triethylamine using the standard conditions afforded a 90% yield of elimination product **93**; none of the desired tetrahydroisoquinoline was observed. Elimination also predominated over alkylation when the bromoester **37** was subjected to these reaction conditions. It was observed, however, that the application of Boeckman's approach[19] allowed for the desired annulation to proceed. Reaction of **37** with potassium phthalimide in dimethyl-formamide,[51] followed by hydrazinolysis of phthalimide derivative **94** in ethanol, cleanly afforded tetrahydroisoquinoline product **96** (72%) presumably through formation of intermediate primary amine **95** which underwent subsequent ring closure.

Structure Elucidation of Products 89, 90, 91, and 92. The stereochemical structures of products **89**, **90**, **91**, and **92** were assigned on the basis of the analysis of a series of comparative ^{1}H-n.O.e. and ^{1}H-NMR coupling constant studies[52,53,54,55] that were carried out on each pair of products. The results of these studies on products **89** and **90** are shown in Tables III and IV. Following the aquisition of additional ^{1}H selective decoupling experiments to verify the initial proton assignments, the COSY and HETCOR 2D spectra on each of these products were recorded. Comparison of the H_{7a}-H_1 coupling constants of **89** and **90** seemed to indicate that the acetate residue moiety in **89** was most likely cis to the ring junction (or exo) because of the larger H_{7a}-H_1 coupling constant in **89** (protons trans) relative to **90** (protons cis). Comparative ^{1}H-n.O.e. determinations[55,56] on **89** and **90** supported the results observed in the above studies. For use in these determinations, degassed and evacuated samples of **89** and **90** (0.024 *M* in $CDCl_3$) were prepared using the freeze-thaw cycle as described by Neuhaus and Williamson.[55] Three identical sealed samples of both **89** and **90** were prepared in this manner. Each sample was then submitted to three separate ^{1}H-n.O.e. determinations. For all three of the samples studied for both **89** and **90** (a total of nine

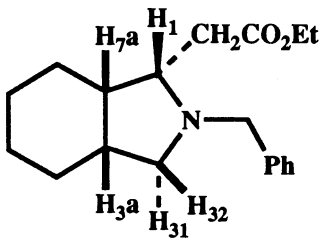
determinations for each compound), the ^{1}H-n.O.e. results observed were reproducible to within ±0.1% enhancement. In the case of **90**, an ^{1}H-n.O.e. of 7% was observed between protons H_1 and H_{7a} and a 3% enhancement was observed between protons H_1 and H_{32} thus suggesting that H_1, H_{7a}, and H_{32} were all on the same face of the 5-ring. In the case of **89**, however, an ^{1}H-n.O.e. of 3% was observed between protons H_1 and H_{31} indicating their proximity to each other; no enhancement between H_{7a} and H_1 was observed. The structural assignments shown in Tables III and IV are those that best support the results obtained in these comparative ^{1}H-NMR experiments.

TABLE III

SELECTED PROTON ASSIGNMENTS AND OBSERVED COUPLING CONSTANTS FOR BICYCLIC NITROGEN PRODUCTS **89** AND **90**.



89



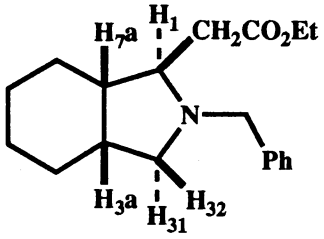
90

	Product	
Coupled Protons	**89**[a]	**90**[a]
H_{32} - H_{31}	11.4	12.1
H_{3a} - H_{31}	6.3	7.8
H_{3a} - H_{32}	5.7	6.6
H_{7a} - H_1	5.4	3.8

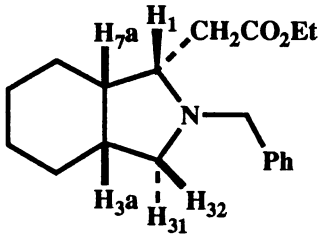
[a] J (Hz)

TABLE IV

OBSERVED ^{1}H-N. O. E. INTERACTIONS FOR SELECTED PROTON PAIRS OF NITROGEN PRODUCTS **89** AND **90**.



89



90

	Product	
Proton Interaction[a]	**89**	**90**
CH_2 - H_{7a}	3 %	0 %
H_1 - H_{7a}	0 %	7 %
H_1 - H_{3a}	0 %	4 %
H_{7a} - H_{3a}	6 %	7 %
H_1 - H_{31}	3 %	0 %
H_1 - H_{32}	0 %	3 %

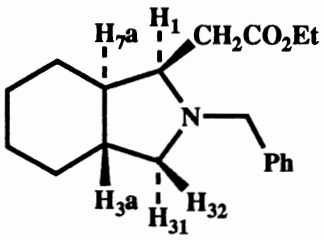
[a]% Enhancement

The same structural assignment strategy was carried out on **91** and **92**. The results of these studies are shown in Tables V and VI. The smaller magnitude of the H_{7a}-H_1 coupling constant in **91** relative to **92** indicated that the protons H_{7a} and H_1 of **91** were most probably on the same face of the 5-ring; this observation was further substantiated by an observed ^{1}H-n.O.e. of 5% between protons H_{7a} and H_1 and a 3% enhancement between protons H_1 and H_{31} in **91**. Conversely, in product **92** no enhancement between

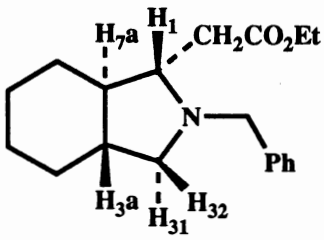
protons H_{7a} and H_1 or protons H_1 and H_{31} was observed; in addition, a ^{1}H-n.O.e. of 4% was observed between protons H_1 and H_{3a} as well as a 4% enhancement between protons

TABLE V

SELECTED PROTON ASSIGNMENTS AND OBSERVED COUPLING CONSTANTS FOR BICYCLIC NITROGEN PRODUCTS **91** AND **92**.



91



92

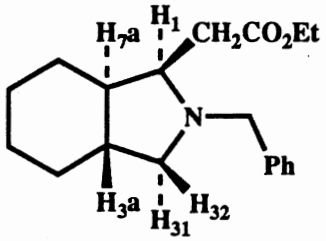
	Product	
Coupled Protons	**91**[a]	**92**[a]
H_{32} - H_{31}	9.6	10.2
H_{3a} - H_{31}	7.4	8.4
H_{3a} - H_{32}	6.2	5.1
H_{7a} - H_1	6.4	7.8

[a] J (Hz)

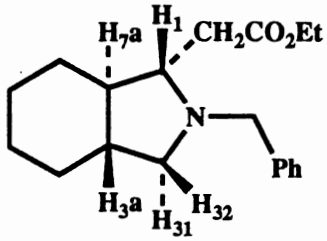
H_1 and H_{32} thus implying that H_1, H_{3a}, and H_{32} are all on the same face of the 5-ring. The structural assignments for **91** and **92** shown in Tables V and VI are those that best support the data obtained in these comparative ^{1}H-NMR experiments.

TABLE VI

OBSERVED ^{1}H-N. O. E. INTERACTIONS FOR SELECTED PROTON PAIRS OF NITROGEN PRODUCTS **91** AND **92**.



91



92

	Product	
Proton Interaction[a]	**91**	**92**
CH_2 - H_{7a}	0 %	5 %
H_1 - H_{7a}	5 %	0 %
H_1 - H_{3a}	0 %	4 %
H_{7a} - H_{3a}	0 %	0 %
H_1 - H_{31}	3 %	0 %
H_1 - H_{32}	0 %	4 %

[a]% Enhancement

Mechanistic Description of the Nitrogen Heterocyclic Ring Formation Process. Two mechanistic scenarios are possible to describe the nitrogen heterocyclization process. In the formation of cyclic amines, it is conceivable that the S_N2 process occurs first followed by the Michael addition reaction but it is also possible that the reverse sequence with the Michael addition being the initial step in the reaction pathway may be operating. To determine which of these processes is responsible for product formation, an equimolar mixture of 1-iodohexane and ethyl crotonate was treated with

benzylamine and triethylamine according to the standard procedure. The reaction was monitored by GC for the selective disappearance of reactants. After 12 h, the benzylamine and 1-iodohexane were totally consumed. The ethyl crotonate was also consumed but to a much lesser extent. The results of this experiment suggest that the S_N2 displacement process is the initial step in the reaction mechanism.

In view of these observations, one can envision the mechanism as shown in Figure 18 to be operating. The reaction of the haloester **97** with the primary amine proceeds

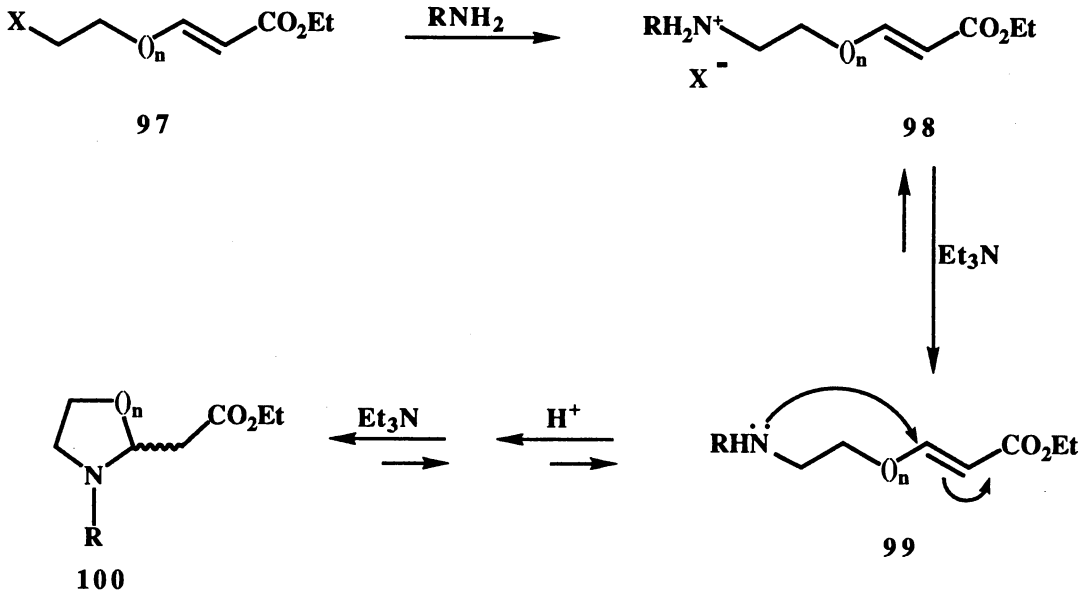


Figure 18. Mechanism of the Formation of Nitrogen Heterocycles by a Tandem S_N2-Michael Addition Sequence.

through an S_N2 displacement of the halogen by the lone electron pair of the primary nitrogen atom to yield a secondary aminium halide salt **98** which then reacts with triethylamine to afford the secondary amine **99**. The intermediate amine **99** then initiates

an intramolecular Michael addition process onto the acrylate acceptor to afford the cyclic amine product **100**. In cases where the alcohol solvent is different than the alkyloxy group of the ester functionality, for example in substrates **27** and **28**, transesterification of the acrylate ester moiety may also occur.

Preparation of 5- and 6-Ring Sulfur Heterocycles. Several routes to the analogous sulfur heterocycles were also evaluated. An initial attempt involved the reaction of the haloester substrate **97** with Na_2S in ethanol.[57] The approach that was employed is illustrated in Figure 19. It was thought *a priori* that the sulfide ion would assume a role similar to that shown by nitrogen, i.e. displacing the halide by an S_N2 process to generate a thiolate intermediate **101** which would undergo a subsequent intramolecular Michael addition reaction to form the sulfur product **102**. Attempts using substrate **33** as a test case, however, produced a complex mixture of products.

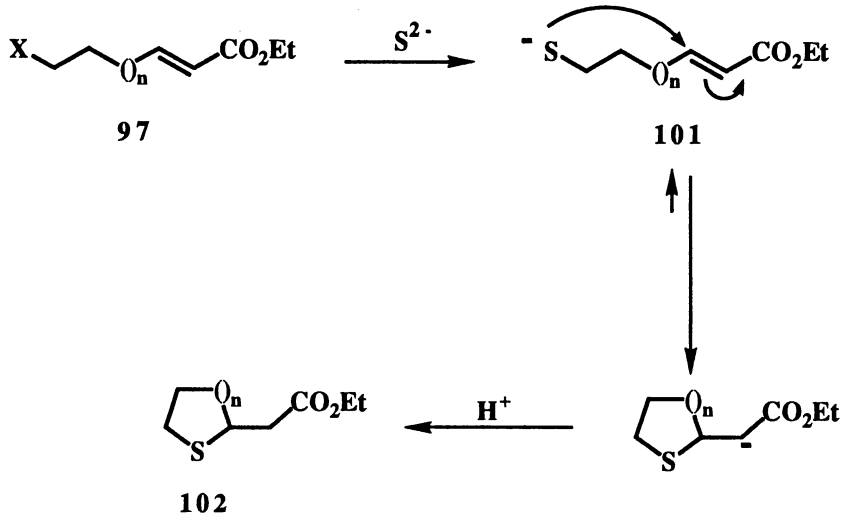


Figure 19. An Attempted Formation of Sulfur Heterocycles Using Sodium Sulfide.

A successful method was developed for the generation of 5- and 6-ring sulfur heterocycles and is shown in Figure 20 for substrate **33**. The method proceeded by a two-step process involving reaction of the halo ester **33** with thiourea in ethanol solvent to afford the isothiuronium salt[58] **103** which was then hydrolyzed in aqueous base[58] to afford the sulfur product **110** in the form of its carboxylic acid.

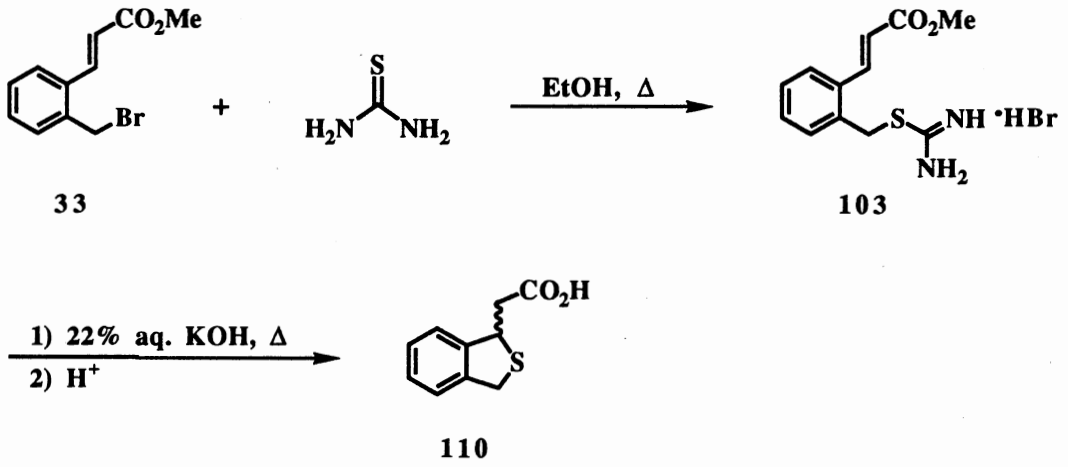
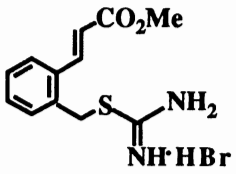
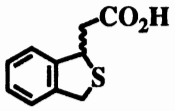
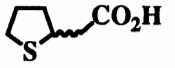
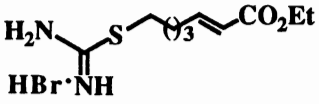
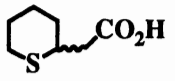
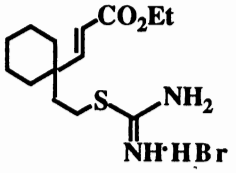
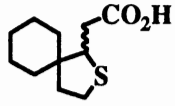
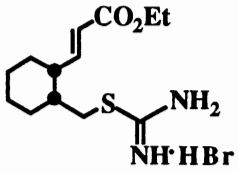
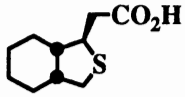
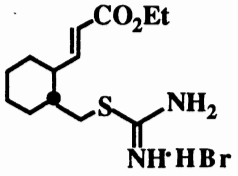
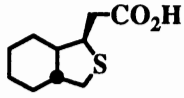
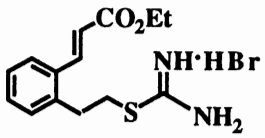
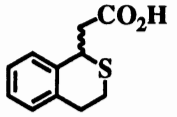


Figure 20. The Preparation of Sulfur Heterocycle **110** by a Tandem S_N2-Michael Addition Reaction Sequence.

The results of this study on the tandem S_N2-hydrolysis-Michael addition approach to sulfur heterocycles are shown in Table VII. The bromoester was first converted to its isothiuronium salt by reaction with thiourea in ethanol solvent. Although it proved possible to effect the entire reaction sequence in a single operation, the isothiuronium salts were generally isolated and characterized. Treatment of the isolated salt with 22% aqueous potassium hydroxide at reflux for 8 h resulted in hydrolysis of the isothiuronium moiety to form the thiolate intermediate which then underwent an intramolecular Michael addition to the terminal acrylate acceptor to afford the sulfur product after an acidic workup. In this

TABLE VII

THE FORMATION OF SULFUR HETEROCYCLES BY A TANDEM S_N2-MICHAEL ADDITION REACTION SEQUENCE.

Bromide	Isothiuronium Salt[a]		Sulfur Product		Yield[a]
33		103		110	68%
23		104		111	59%
24		105		112	69%
82		106		113	71%
46		107		114	74%
55		108		115	76%
37		109		116	73%

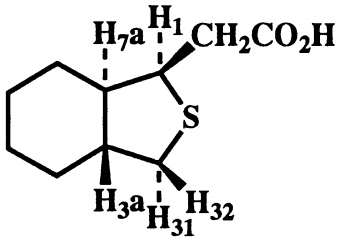
[a]Overall yields refer to isolated, purified products based on starting bromide.

method, the sulfur products were isolated as the carboxylic acid derivatives because of base hydrolysis of the starting ester functionality during the course of the reaction. The method as devised proceeds smoothly to afford essentially pure products with yields in the range of 59-76%. With the exception of **111**, all of the sulfur products were isolated as white solids that were easily purified by recrystallization.

Structure Elucidation of Products 114 and 115. Following the same structural assignment strategy as that used for nitrogen products **89-92**, evaluations of ^{1}H-n.O.e. and ^{1}H-NMR coupling constants were carried out on sulfur product **115** as well. The results are shown in Tables VIII and IX. In the ^{1}H-n.O.e. studies, a 4%

TABLE VIII

SELECTED PROTON ASSIGNMENTS AND OBSERVED COUPLING COUPLING CONSTANTS FOR SULFUR HETEROCYCLE **115**.



115

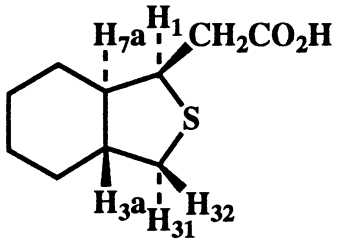
Coupled Protons	Product **115**[a]
H_{32} - H_{31}	9.6
H_{3a} - H_{31}	6.8
H_{3a} - H_{32}	6.0
H_{7a} - H_1	7.2

[a] J (Hz)

enhancement was observed to occur between protons H_{7a} and H_1 and a 3% enhancement was observed for protons H_1 and H_{31} thus implying that H_{7a}, H_1, and H_{31} are all on the same face of the 5-ring. The structural assignment for **115** shown in Tables VIII and IX is the one which best supports the data obtained in these ^{1}H-NMR experiments.

TABLE IX

OBSERVED ^{1}H-N. O. E. INTERACTIONS FOR SELECTED PROTON PAIRS IN SULFUR HETEROCYCLE **115**.



115

Proton Interaction[a]	Product **115**
CH_2 - H_{7a}	0 %
H_1 - H_{7a}	4 %
H_1 - H_{3a}	0 %
H_{7a} - H_{3a}	0 %
H_1 - H_{31}	3 %
H_1 - H_{32}	0 %

[a]% Enhancement

The *exo* stereochemistry of the acetate residue of sulfur product **114** was assigned from a single crystal X-ray structure obtained on crystals of **114** grown in aqueous

ethanol. The CHEM3D diagram of **114** is illustrated in Figure 21.

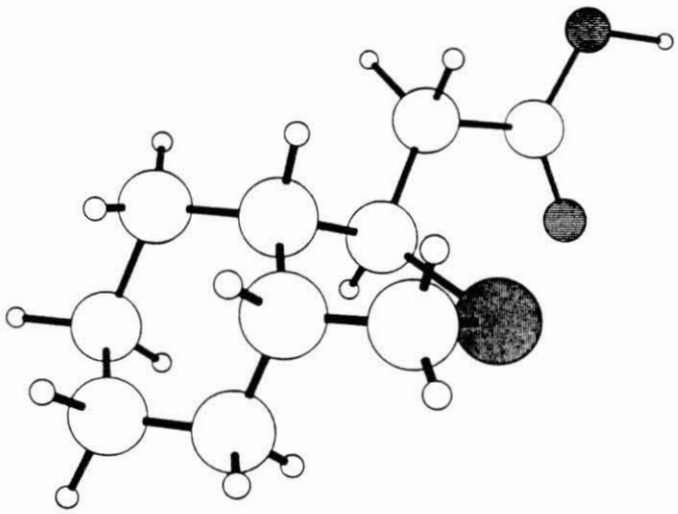


Figure 21. The CHEM3D Diagram for Sulfur Heterocycle **114**.

Mechanistic Description of the Sulfur Heterocyclic Ring Formation Process. Since the isothiuronium salts were isolated as intermediates in the sulfur heterocyclization process, the initial stages of the reaction are less ambiguous. There exist, however, two reaction pathways that the second hydrolysis step in the sequence could potentially follow to afford the observed cyclized products. The strong base required for the second stage of the method performs three functions: 1) neutralization of the isothiuronium halide salt, 2) hydrolysis of the ester functionality and 3) cleavage of the amidine group to afford the free thiolate that closes onto the Michael acceptor moiety. To determine the sequence of steps leading to the observed cyclic products, a control experiment was conducted where equimolar amounts of benzylisothiuronium bromide (**117**) and ethyl cinnamate (**118**) were exposed to 22% aqueous potassium hydroxide at

23°C using the same concentrations as described in the method devised (see Figure 22). Periodic monitoring of the reaction mixture by TLC indicated that ester **118** was saponified (to afford carboxylate **119**) more readily under these conditions than **117** was hydrolyzed (to afford thiolate **120**). This observation suggests that the Michael addition process most likely occurs onto the acrylic acid moiety *after* the base hydrolysis of the ester group. This appears to be one of a very few reported additions to monoactivated acrylic acids.[59]

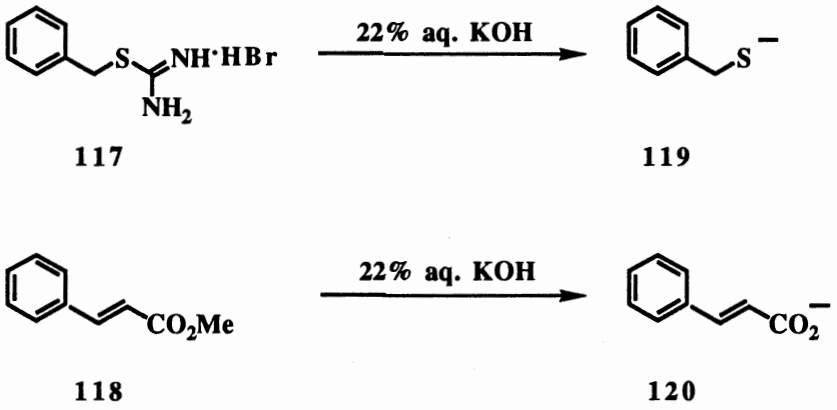


Figure 22. Reaction of **117** and **118** with Potassium Hydroxide.

In view of these observations, one can envision the mechanism shown in Figure 23 to be operating in the formation of sulfur heterocycles. The acid-base reaction of isothiuronium halide salt **121** with hydroxide ion initially yields the neutral amidine intermediate **122** which then undergoes base hydrolysis of the ester functionality to afford carboxylate **123**. Subsequent base hydrolysis of the amidine group generates dianion **124** which then cyclizes by Michael addition of the thiolate to the acrylic acid moiety to yield the

carboxylate dianion **125**.[60] Protonation of **125** by water then affords the carboxylate intermediate **126** which, after acidic workup, gives the observed cyclized product **127**.

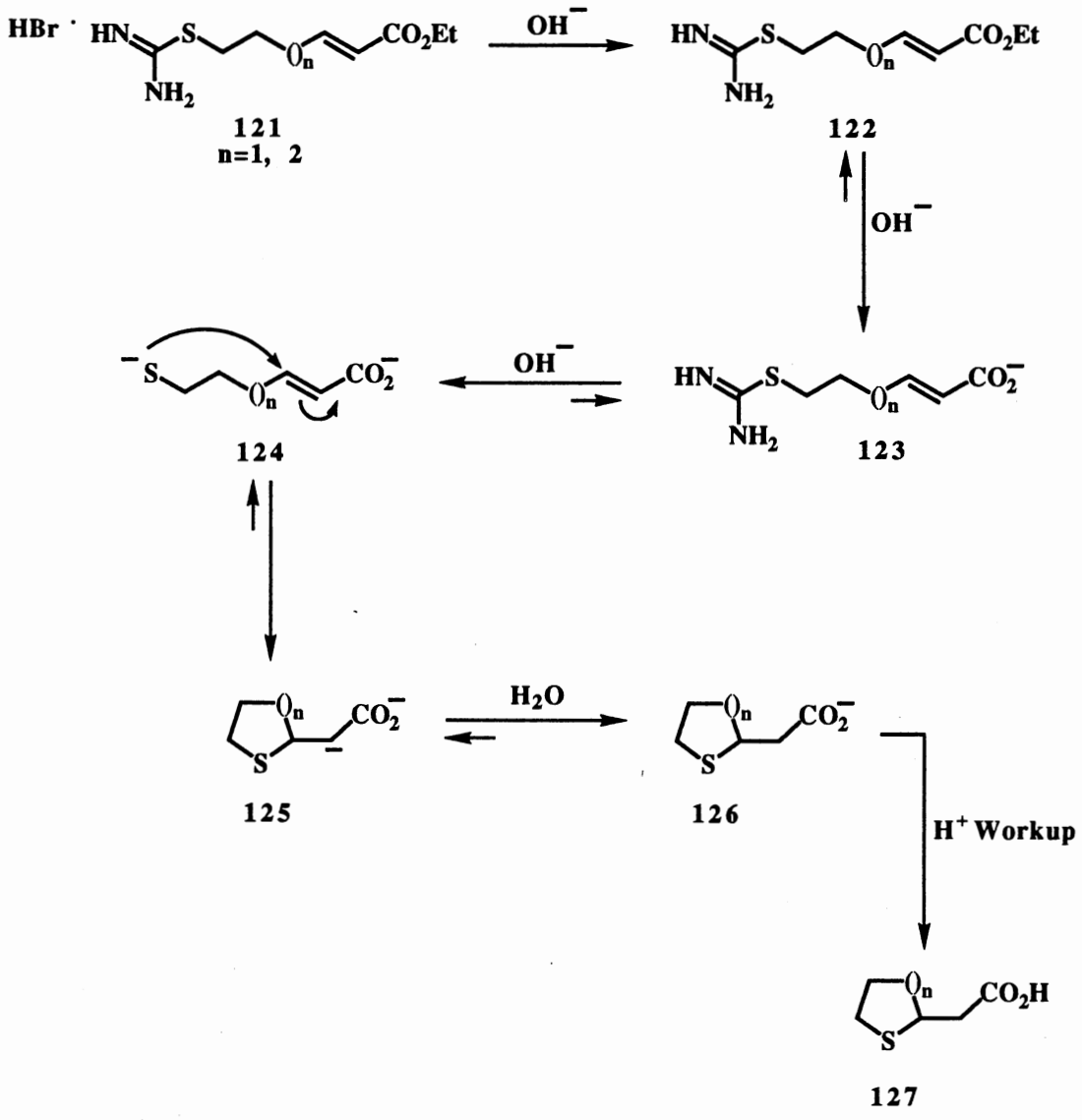


Figure 23. Mechanism of the Formation of Sulfur Heterocycles by a Tandem S_N2-Michael Addition Reaction Sequence.

Experimental

All solvents were distilled prior to use; other reagents were used as received from the vendors. All reactions were run under an atmosphere of dry nitrogen. Ozonolyses were performed using a Welbash T-23 laboratory ozonizer. Reactions were monitored by one of the following methods: 1) TLC on hard layer silica gel GF plates (Analtech No. 21521) with UV or phosphomolybdic acid detection or 2) capillary GC (Varian 3400) with FI detection on a 0.1 mm x 6 m SE-30 column programmed between 40-150°C. Preparative separations were performed using one of the following methods: 1) PTLC on 20 cm x 20 cm silica gel GF plates (Analtech No. 02015) or 2) flash chromatography[61] on silica gel (Grace, grade 62, 60-200 mesh) containing UV active phosphor (Sylvania no. 2282); in each case, band elution was monitored by a hand-held UV lamp. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded with a PE-681 instrument and are referenced to polystyrene. ^{1}H-NMR and ^{13}C-NMR spectra were measured as solutions in deuterated solvents at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively, on a Varian XL-300 or a Varian XLA-400 superconducting FT instrument; chemical shifts are reported in δ units relative to internal Me_4Si. Mass spectra (MS) were obtained using a VG TS-250 instrument; high resolution mass spectra (HRMS) were obtained using a VG ZAB-2SE. Elemental analyses (± 0.4%) were performed by Galbraith Laboratories, Knoxville, TN.

General Procedure for the Preparation of ω-Bromo-*n*-alkanols from Cyclic Ethers Using Hydrobromic Acid (15 and 16). The procedure of Vedejs and co-workers[36] was followed. To 4.15 mol of refluxing tetrahydrofuran (in the preparation of **15**) or tetrahydropyran (in the preparation of **16**) was added 152 mL of 48% aqueous hydrobromic acid (226.5 g, 108.7 g HBr, 1.34 mol HBr) dropwise over the course of 3 h with vigorous stirring. Following the addition, the mixture was refluxed with continued stirring for 2 h and cooled to 25°C. The mixture was neutralized with solid $NaHCO_3$, partitioned with water, washed with water and saturated aqueous NaCl, dried

over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the bromoalkanol as a clear light yellow oil that was purified by vacuum distillation. The physical and spectral properties of the products were the following:

4-Bromo-1-butanol (15): 23.2 g (0.161 mol, 12%); bp 62-64°C (0.5 mm Hg); IR (thin film) 3540-3100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 1 H), 3.69 (m, 2 H), 3.46 (m, 2 H), 1.96 (m, 2 H), 1.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 61.8, 33.6, 30.9, 29.1; HRMS, *m/e* for $C_4H_9O^{79}Br$: calcd, 143.9211; found, 143.9208; *m/e* for $C_4H_9O^{81}Br$: calcd, 145.9190; found, 145.9188.

5-Bromo-1-pentanol (16): 31.7 g (0 201 mol, 15%); bp 73-75°C (0.5 mm Hg); IR (thin film) 3540-3100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (m, 2 H), 3.43 (m, 2 H), 1.98 (m, 3 H), 1.58 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 62.5, 33.7, 32.4, 31.7, 24.4; HRMS, *m/e* for $C_5H_{11}O^{79}Br$: calcd, 157.9367; found, 157.9364; *m/e* for $C_5H_{11}O^{81}Br$: calcd, 159.9347; found, 159.9342.

General PCC Oxidation Procedure for the Preparation of ω-Halo-*n*-alkanals from ω-Halo-*n*-alkanols (19, 20, 21, and 22). The general procedure of Corey and Suggs[37] was followed. To a stirred and cooled (0-5°C) slurry of 105.0 g (487 mmol) of pyridinium chlorochromate and 6.97 g (85 mmol) of sodium acetate in 325 mL of methylene chloride was added a solution of 250 mmol of the haloalkanol in 325 mL of methylene chloride dropwise over the course of 2 h with stirring. After 2.5 h of continued stirring at 25°C, 700 mL of petroleum ether was added in one portion and the resulting mixture was stirred for 30 min. The mixture was suction filtered through a 20 cm x 12 cm plug of Celite® in a large frit and the collected filtrate was concentrated *in vacuo* to yield the haloalkanal product as a clear light brown oil that was used without further purification. The physical and spectral properties of the products were the following:

4-Chloro-1-butanal (21): 21.3 g (250.0 mmol, 80%); IR (thin film) 2720, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.81 (bs, 1 H), 3.60 (t, 2 H, J = 6.3 Hz), 2.68 (t, 2 H,

J = 6.9 Hz), 2.11 (tt, 2 H, J = 6.9, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 200.8, 43.9, 40.6, 24.6; HRMS, *m/e* for $C_4H_7O^{35}Cl$: calcd, 106.0185; found, 106.0184; *m/e* for $C_4H_7O^{37}Cl$: calcd, 108.0156; found, 108.0152.

5-Chloro-1-pentanal (22): 22.9 g (190.0 mmol, 76%); IR (thin film) 2725, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.72 (bs, 1 H), 3.62 (m, 2 H), 2.52 (m, 2 H), 1.98 (m, 2 H), 1.82 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 200.5, 43.9, 33.2, 31.7, 20.3; HRMS, *m/e* for $C_5H_9O^{35}Cl$: calcd, 120.0342; found, 120.0339; *m/e* for $C_5H_9O^{37}Cl$: calcd, 122.0312; found 122.0310.

4-Bromo-1-butanal (19): 27.6 g (183.0 mmol, 73%); IR (thin film) 2730, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.82 (bs, 1 H), 3.47 (t, 2 H, J = 6.3 Hz), 2.69 (t, 2 H, J = 6.9 Hz), 2.19 (tt, 2 H, J = 6.9, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 200.7, 42.0, 32.7, 24.9; HRMS, *m/e* for $C_4H_7O^{79}Br$: calcd, 149.9680; found, 149.9684; *m/e* for $C_4H_7O^{81}Br$: calcd, 151.9660; found, 151.9661.

5-Bromo-1-pentanal (20): 32.7 g (198.0 mmol, 79%); IR (thin film) 2720, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.78 (bs, 1 H), 3.42 (m, 2 H), 2.50 (m, 2 H), 1.90 (m, 2 H), 1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.7, 42.7, 32.9, 31.8, 20.5; HRMS, *m/e* for $C_5H_9O^{79}Br$: calcd, 163.9837; found, 163.9834; m/e for $C_5H_9O^{81}Br$: calcd, 165.9816; found, 165.9815.

General Wittig Olefination Procedure for the Preparation of Ethyl (*E*)-ω-Halo-2-alkenoates from ω-Halo-*n*-alkanals (23, 24, 25, and 26). A 150-mL benzene solution of 79.0 mmol of the haloalkanal and 27.5 g (79.0 mmol) of ethyl (triphenylphosphoranylidene)acetate was refluxed for 14 h with stirring. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light brown solid residue. The residue was subjected to flash vacuum chromatography[62] through a 20 cm x 12 cm plug of silica gel in a large frit using 90:10 hexane/ether. Concentration of the collected eluent afforded the crude chloro enoate ester product as a clear light yellow oil that was purified

by vacuum distillation. The physical and spectral properties of the products were the following:

Ethyl (*E*)-6-Chloro-2-hexenoate (25): 9.90 g (56.1 mmol, 71%); bp 68-72°C (1.0 mm Hg); IR (thin film) 1735, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (dt, 1 H, J = 15.9, 6.7 Hz), 5.88 (d, 1 H, J = 15.9 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.56 (m, 2 H), 2.38 (m, 2 H), 1.95 (m, 2 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 146.9, 122.5, 60.3, 44.0, 30.7, 29.2, 14.3; HRMS, *m/e* for $C_8H_{13}O_2{}^{35}Cl$: calcd, 176.0604; found, 176.0607; *m/e* for $C_8H_{13}O_2{}^{37}Cl$: calcd, 178.0574; found, 178.0572.

Ethyl (*E*)-7-Chloro-2-heptenoate (26): 10.98 g (57.7 mmol, 73%); bp 74-76°C (1.0 mm Hg); IR (thin film) 1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (dt, 1 H, J = 15.8, 6.4 Hz), 5.85 (d, 1 H, J = 15.8 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.55 (m, 2 H), 2.26 (m, 2 H), 1.81 (m, 2 H), 1.63 (m, 2 H), 1.27 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.1, 147.9, 121.6, 59.9, 44.3, 31.6, 31.0, 25.0, 14.0; HRMS, *m/e* for $C_9H_{15}O_2{}^{35}Cl$: calcd, 190.0760; found, 190.0762; *m/e* for $C_9H_{15}O_2{}^{37}Cl$: calcd, 192.0731; found, 192.0728.

Ethyl (*E*)-6-Bromo-2-hexenoate (23): 12.39 g (56.1 mmol, 71%); bp 75-77°C (1.0 mm Hg); IR (thin film) 1725, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (dt, 1 H, J = 15.8, 6.7 Hz), 5.89 (d, 1 H, J = 15.8 Hz), 4.20 (q, 2 H, J = 6.9 Hz), 3.42 (m, 2 H), 2.39 (m, 2 H), 2.04 (m, 2 H), 1.28 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 147.0, 122.1, 61.0, 32.5, 30.7, 30.4, 14.1; HRMS, *m/e* for $C_8H_{13}O_2{}^{79}Br$: calcd, 220.0099; found, 220.0093; *m/e* for $C_8H_{13}O_2{}^{81}Br$: calcd, 222.0078; found, 222.0072.

Ethyl (*E*)-7-Bromo-2-heptenoate (24): 11.89 g (50.6 mmol, 64%); bp 85-87°C (1.0 mm Hg); IR (thin film) 1730, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 6.8 Hz), 5.84 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.42 (m, 2 H), 2.24 (m, 2 H), 1.89 (m, 2 H), 1.63 (m, 2 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 148.0, 121.8, 60.1, 33.2, 31.9, 31.1, 26.4, 14.2; HRMS, *m/e* for

$C_9H_{15}O_2{}^{79}Br$: calcd, 234.0255; found, 234.0255; *m/e* for $C_9H_{15}O_2{}^{81}Br$: calcd, 236.0235; found, 236.0236.

General Finkelstein Halogen Exchange Procedure for the Formation of Alkyl Iodides (27 and 28). A 375-mL acetone solution of 57.0 mmol of the chloro enoate ester and 84.9 g (570 mmol) of sodium iodide was stirred at reflux for 18 h. The reaction mixture was cooled to 25°C and concentrated *in vacuo* to afford a solid yellow residue. The residue was dissolved in 200 mL of water and extracted twice with ether. The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield the iodo enoate ester as a clear light yellow oil that was used without further purification. The physical and spectral properties of the products were the following:

Ethyl (*E*)-6-Iodo-2-hexenoate (27): 15.10 g (56.3 mmol, 99%); IR (thin film) 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (dt, 1 H, J = 15.6, 7.2 Hz), 5.88 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 7.5 Hz), 3.19 (m, 2 H), 2.35 (m, 2 H), 1.98 (m, 2 H), 1.29 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 146.5, 122.6, 60.2, 32.7, 31.4, 14.3, 5.5; HRMS, *m/e* for $C_8H_{13}O_2I$: calcd, 267.9960; found, 267.9961.

Ethyl (*E*)-7-Iodo-2-heptenoate (28): 15.93 g (56.5 mmol, 99%); IR (thin film) 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 7.5 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.19 (m, 2 H), 2.23 (m, 2 H), 1.86 (m, 2 H), 1.59 (m, 2 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 148.0, 121.8, 60.2, 32.7, 30.9, 28.8, 14.2, 6.1; HRMS, *m/e* for $C_9H_{15}O_2I$: calcd, 282.0117; found, 282.0114.

Methyl (*E*)-2-(Methyl)cinnamate (32). A 200-mL benzene solution of 12.0 g (100 mmol) of 2-methylbenzaldehyde (**31**) and 33.4 g (100 mmol) of methyl (triphenylphosphoranylidene)acetate was refluxed for 14 h with stirring. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a white solid residue. The residue was subjected to flash vacuum chromatography[62] through a 20 cm x 12 cm plug of silica gel in a large

frit using 90:10 hexane/ether. Concentration of the collected eluent afforded a light yellow thin oil that was purified by vacuum distillation to afford 15.66 g (89.0 mmol, 89%) of **32** as a clear colorless liquid, bp 99-100°C (0.5 mm Hg). The spectral data for **32** were: IR (thin film) 1725, 1640, 1600, 1575, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (d, 1 H, J = 15.9 Hz), 7.52 (d, 1 H), 7.23 (m, 3 H), 6.35 (d, 1 H, J = 15.9 Hz), 3.79 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.3, 142.4, 137.5, 133.2, 130.6, 129.9, 126.3, 126.2, 118.7, 51.5, 19.6; HRMS, *m/e* for $C_{11}H_{12}O_2$: calcd,176.0837; found, 176.0837.

Methyl (*E*)-2-(Bromomethyl)cinnamate (33). The procedure of Greenwood and co-workers [38] was followed. A mixture of 8.80 g (50.0 mmol) of **32**, 8.90 g (50.0 mmol) of *N*-bromosuccinimide and 50 mg of benzoyl peroxide in 60 mL of carbon tetrachloride was irradiated to reflux with a spotlamp (Westinghouse 150w reflector spotlight) with stirring for 2.5 h. The mixture was then cooled to 25°C and 60 mL of pentane was added in one portion. The resulting succinimide by-product was removed by suction filtration and washed with two 50 mL portions of pentane. The collected washings were concentrated *in vacuo* to afford the crude bromide as a light-yellow solid which was purified by recystallization from methanol to yield 8.79 g (34.5 mmol, 69%) of **33** as a white solid, mp 86-87°C. The spectral data for **33** were: IR ($CHCl_3$) 1715, 1630, 1600, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (d, 1 H, J = 15.9 Hz), 7.59 (m, 1 H), 7.36 (m, 3 H), 6.45 (d, 1 H, J = 15.9 Hz), 4.60 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.0, 140.7, 136.6, 133.7, 130.7, 130.3, 129.3, 127.2, 120.6, 51.8, 30.5; HRMS, *m/e* for $C_{11}H_{11}O_2{}^{79}Br$: calcd, 253.9942; found, 253.9939; *m/e* for $C_{11}H_{11}O_2{}^{81}Br$: calcd, 255.9922; found, 255.9921.

Isochroman (35). The procedure of Rieche and Schmitz[39] was used. A stirred and cooled (0-5°C) mixture of 24.4 g (200 mmol) of 2-phenylethanol (**34**) and 7.5 g (250 mmol) of dry paraformaldehyde was treated with a strong stream (90 bubbles/min) of HCl gas until the paraformaldehyde dissolved and two layers were observed to form (*ca.* 2 h). The resulting mixture was allowed to warm to 25°C and was then treated with a thin stream

(30 bubbles/min) of HCl gas for 6 h with continued stirring. The mixture was cooled to 0-5°C and a solution of 10 g of NaOH in 50 mL of water was cautiously added. The mixture was then refluxed for 2 h with stirring. After cooling to 25°C, the resulting aqueous mixture was extracted twice with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a yellow oil which was purified by vacuum distillation to yield 22.8 g (170 mmol, 85%) of **35** as a clear colorless liquid, bp 69-70°C (1.0 mm Hg). The spectral data for **35** were: IR (thin film) 3060, 3020, 1600, 1560, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (m, 3 H), 6.95 (m, 1 H), 4.75 (s, 2 H), 3.95 (t, 2 H, J = 5.7 Hz), 2.83 (t, 2 H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 135.0, 133.3, 129.0, 126.4, 126.0, 124.5, 68.0, 65.5, 28.4; HRMS, *m/e* for $C_9H_{10}O$: calcd, 134.0731; found, 134.0729.

2-(2-Bromoethyl)benzaldehyde (36). The procedure of Rieche and Schmitz[39] was used. A stirred solution of 10.0 g (74.6 mmol) of **35** in 50 mL of carbon tetrachloride at 25°C was treated with 12.0 g (74.6 mmol, 3.86 mL) of bromine over the course of 1 h. Following the addition, the resulting mixture was refluxed with stirring for 1 h. The mixture was concentrated *in vacuo* and the isolated residue was treated with 15 mL of 48% aqueous hydrobromic acid. The resulting slurry was heated to reflux for 5 min with vigorous stirring. The mixture was then cooled to 25°C and extracted twice with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a brown oil. Vacuum distillation using a Kugelrohr apparatus yielded 10.2 g (48.0 mmol, 64%) of **36** as a clear colorless oil, bp 120-123°C (0.5 mm Hg). The spectral data for **36** were: IR (thin film) 2735, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.14 (bs, 1 H), 7.82 (m, 1 H), 7.56 (m, 1 H), 7.48 (m, 1 H), 7.33 (m, 1 H), 3.59 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 193.0, 140.5, 134.5, 133.8, 132.1, 130.2, 127.7,

36.3, 32.9; HRMS, *m/e* for $C_9H_9O^{79}Br$: calcd, 211.9837; found, 211.9834; *m/e* for $C_9H_9O^{81}Br$: calcd, 213.9816; found, 213.9814.

Ethyl (*E*)-2-(2-Bromoethyl)cinnamate (37). A 100-mL benzene solution of 8.25 g (38.8 mmol) of **36** and 13.5 g (38.8 mmol) of ethyl (triphenylphosphoranylidene)acetate was refluxed for 16 h with stirring. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light tan solid residue. The solid was subjected to flash vacuum chromatography[62] through a 20 cm x 12 cm plug of silica gel in a large frit using 90:10 hexane/ether. Concentration of the collected eluent afforded a yellow oil which was purified by column chromatography on a 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing the concentrations of ether in hexane. The first and largest band, eluted with 4% ether in hexane, afforded 7.46 g (26.4 mmol, 68%) of **37** as a clear colorless oil after concentration. The spectral data for **37** were: IR (thin film) 3050, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 15.6 Hz), 7.58 (m, 1 H), 7.29 (m, 3 H), 6.39 (d, 1 H, J = 15.6 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 3.51 (t, 2 H, J = 7.5 Hz), 3.31 (t, 2 H, J = 7.5 Hz), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 141.1, 138.2, 133.3, 130.6, 130.2, 127.7, 127.0, 120.7, 60.7, 36.5, 32.1, 14.4; HRMS, *m/e* for $C_{13}H_{15}O_2{}^{79}Br$: calcd, 282.0255; found, 282.0249; *m/e* for $C_{13}H_{15}O_2{}^{81}Br$: calcd, 284.0235; found, 284.0237.

Ethyl (*E*)-2-(2-Iodoethyl)cinnamate (38). A 75-mL acetone solution of 2.83 g (10.0 mmol) of **37** and 15.0 g (100 mmol) of sodium iodide was stirred at reflux for 14 h. The reaction mixture was cooled to 25°C and concentrated *in vacuo* to afford a solid yellow residue. The residue was dissolved in 75 mL of water and extracted twice with ether. The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield 3.02 g (9.20 mmol, 92%) of **38** as a clear light yellow oil that was used without further purification. The spectral data for **38** were: IR (thin film) 3050, 1710, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (d, 1 H, J = 15.9 Hz), 7.56 (m, 1 H), 7.31

(m, 2 H), 7.21 (m, 1 H), 6.38 (d, 1 H, J = 15.9 Hz), 4.27 (q, 2 H, J = 7.2 Hz), 3.28 (m, 4 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 141.1, 139.9, 133.0, 130.2 (2), 127.6, 127.0, 120.6, 60.7, 37.5, 14.4, 4.5; HRMS, *m/e* for $C_{13}H_{15}O_2I$: calcd, 330.0117; found, 330.0116.

(1*R,2*S**)-(±)-1,2-Cyclohexanedimethanol (42).** The procedure of Photis and Paquette[40] was used. To a stirred slurry of 1.48 g (39 mmol) of lithium aluminum hydride ($LiAlH_4$) in 150 mL of dry tetrahydrofuran (THF) was added a solution of 5.00 g (32.5 mmol) of *cis*-1,2-cyclohexanedicarboxylic anhydride (**41**) in 30 mL of dry THF over the course of 15 min and the resulting mixture was maintained at reflux for 3 h. The reaction mixture was cooled (0-5°C) and 20 mL of a freshly prepared solution of saturated aqueous Na_2SO_4 was cautiously added dropwise with continued stirring and cooling. The insoluable aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite® and were washed with several portions of hot THF. The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield 4.40 g (31 mmol, 94%) of **42** as a clear colorless thick oil which was used without further purification. The spectral data for **42** were: IR (thin film) 3600-3000, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (bs, 2 H), 3.69 (m, 2 H), 3.53 (m, 2 H), 1.92 (m, 2 H), 1.62-1.30 (complex, 8 H); ^{13}C NMR ($CDCl_3$) δ 63.9, 39.8, 27.1, 23.9; HRMS, *m/e* for $C_8H_{16}O_2$: calcd, 144.1150; found, 144.1149.

(1*S,2*R**)-(±)-Diethyl 1,2-Cyclohexanedicarboxylate (49).** The general procedure of Price and Schwartz[44] was followed. A 100-mL ethanol solution of 15.4 g (100 mmol) of **41** and 5 mL of concentrated sulfuric acid was refluxed for 18 h with stirring. The mixture was cooled to 25°C and 50 mL of saturated aqueous $NaHCO_3$ was cautiously added in small portions. The ethanol was then removed by rotary evaporation under vacuum and the resulting aqueous mixture was extracted twice with ether. The combined ether extracts were washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to

yield a light yellow oil which was purified by vacuum distillation to afford 20.3 g (89.0 mmol, 89%) of **49** as a clear colorless liquid, bp 95-96°C (0.5 mm Hg). The spectral data for **49** were: IR (thin film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (q, 4 H, J = 7.2 Hz), 2.81 (m, 2 H), 2.00 (m, 2 H), 1.78 (m, 2 H), 1.52 (m, 2 H), 1.41 (m, 2 H), 1.24 (t, 6 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6, 60.2, 42.5, 26.2, 23.7, 14.1; MS (EI/DP): *m/e* (%) 228 (6), 184 (12), 183 (100), 182 (41), 155 (24), 154 (85), 109 (27), 108 (30), 82 (10), 81 (62), 80 (19), 67 (10); HRMS, *m/e* for $C_{12}H_{20}O_4$: calcd, 228.1362; found, 228.1370.

(1*R,2*R**)-(±)-Hexahydrophthalic Acid (50).** The general procedure of Price and Schwartz[44] was followed. A solution of 10.0 g (43.9 mmol) of **49** in 50 mL of 10% ethanolic KOH was refluxed for 1 h with stirring. After this period of reflux, a 20 cm Vigreux distillation apparatus was affixed to the reaction flask and the ethanol was removed by distillation at atmospheric pressure while water (20 mL) was added to the resulting residue in small portions during the course of the process to control the distillation rate. After the ethanol had been removed, a solution of 5.0 g of KOH in 20 mL of water was added and the resulting mixture was refluxed for 12 h with stirring. The mixture was cooled to 25°C and acidified to a pH of *ca.* 2 by the dropwise addition of 6 *M* HCl at 0-5°C. The resulting precipitate was removed by filtration and recrystallized twice from acetone to yield 6.87 g (39.9 mmol, 91%) of **50** as a fine white solid, mp 218-219°C. The spectral data for **50** were: IR ($CHCl_3$) 3630-2780, 1715 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.20 (bs, 2 H), 2.35 (m, 2 H), 1.93 (m, 2 H), 1.69 (m, 2 H), 1.24 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 176.2, 44.4, 28.6, 25.0; MS (CI, isobutane): *m/e* (%) 173 (M+1, 47), 155 (100), 128 (23), 109 (12), 99 (8), 81 (47), 67 (15); HRMS, *m/e* for $C_8H_{12}O_4$: calcd, 172.0736; found, 172.0734.

(1*S,2*S**)-(±)-1,2-Cyclohexanedimethanol (51).** The procedure of Photis and Paquette[40] was followed. To a stirred slurry of 1.66 g (43.9 mmol) of $LiAlH_4$ in 150 mL of dry THF was added a solution of 4.20 g (24.4 mmol) of **50** in 100 mL of

dry THF over the course of 15 min. and the resulting mixture was maintained at reflux for 3 h. The reaction mixture was then cooled (0-5°C) and 25 mL of a freshly prepared solution of saturated aqueous Na_2SO_4 was cautiously added dropwise with continued stirring and cooling. The insoluble aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite® and were washed with several portions of hot THF. The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield 3.17 g (22.0 mmol, 90%) of **51** as a low melting white solid, mp 29-31°C, which was used without further purification. The spectral data for **51** were: IR ($CHCl_3$) 3640-3030, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (bs, 2 H), 3.58 (m, 2 H), 3.46 (m, 2 H), 1.70 (m, 2 H), 1.58 (m, 2 H), 1.25 (m, 4 H), 1.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 67.7, 44.7, 29.8, 26.1; MS (CI, isobutane): *m/e* (%) 145 (M+1, 100), 127 (27), 109 (48), 95 (29), 81 (17), 67 (14); HRMS, *m/e* for $C_8H_{16}O_2$: calcd, 144.1150; found, 144.1151.

General Oxidation (MnO_2) Procedure for the Preparation of Bicyclic Lactols from Diols 42 and 51 (43 and 52). The general procedure of Marner and Jaenicke[41] was followed. A slurry of 65 mmol of the diol (**42** or **51**) and 56.6 g (650 mmol) of activated manganese dioxide (MnO_2) in 200 mL of methylene chloride was stirred at 25°C for 18 h. The resulting mixture was suction filtered through a 20 cm x 12 cm plug of Celite® in a large frit and the collected solids were thoroughly washed with several 150 mL portions of methylene chloride. The collected filtrate was concentrated *in vacuo* to afford the lactol product as a clear thick colorless oil that was used directly. The physical and spectral properties of the products were the following:

(1a*S,6a*S**)-(±)-7-Hydroxy-8-oxabicyclo[4.3.0]nonane (43)**: 7.94 g (55.9 mmol, 86%); IR (thin film) 3560-3100, 2660 (w), 1760 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (m, 1 H), 4.23 (bs, 1 H), 3.72 (m, 2 H), 2.53 (m, 1 H), 2.05 (m, 1 H), 1.57-1.36 (complex, 8 H); ^{13}C NMR ($CDCl_3$) δ 102.5, 70.5, 44.9, 35.1, 24.7, 24.2, 23.3, 21.9; HRMS, *m/e* for $C_8H_{14}O_2$: calcd, 142.0994; found, 142.0989.

(1a*S,6a*R**)-(±)-7-Hydroxy-8-oxabicyclo[4.3.0]nonane (52)**: 8.04 g (56.6 mmol, 87%); IR (thin film) 3550-3100, 1710 (m) cm^{-1}; HRMS, *m/e* for $C_8H_{14}O_2$: calcd, 142.0994; found, 142.0992. An examination of the ^1H NMR and ^{13}C NMR spectra of **34** (both in $CDCl_3$) showed that all three of the expected open and closed isomeric forms of this lactol product were present.

General Wittig Olefination Procedure for the Preparation of Hydroxyesters 44 and 53 from Lactols 43 and 52. A 150-mL benzene solution of 57.0 mmol of the lactol (**43** or **52**) and 19.8 g (56.8 mmol) of ethyl (triphenylphosphoranylidene)acetate was refluxed for 16 h with stirring. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a thick yellow oil. The oil was subjected to flash vacuum chromatography[62] through a 20 cm x 12 cm plug of silica gel in a large frit using 75:25 hexane/ether. Concentration of the collected eluent afforded either a thick colorless or yellow oil which was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing the concentrations of ether in hexane. The physical and spectral properties of the products were the following:

(1*S,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(hydroxymethyl)cyclohexane (44)**: The third and largest band, eluted with 20% ether in hexane, afforded 5.81 g (27.4 mmol, 48%) of **44** as a clear colorless thick oil after concentration. The spectral data for **44** were: IR (thin film) 3600-3140, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (dd, 1 H, J = 15.6, 6.9 Hz), 5.87 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.44 (d, 2 H), 2.68 (m, 1 H), 2.00 (bs, 1 H), 1.84 (m, 1 H), 1.75-1.43 (complex, 7 H), 1.37 (m, 1 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 149.7, 121.7, 64.7, 60.2, 42.5, 39.2, 30.2, 25.0, 24.6, 22.2, 14.2; MS (CI, isobutane): *m/e* (%) 213 (M+1, 24), 182 (9), 167 (100), 149 (11), 121 (10), 81 (10); HRMS, *m/e* for $C_{12}H_{20}O_3$: calcd, 212.1412; found, 212.1418.

(1*R,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(hydroxymethyl)cyclohexane (53)**: The third and largest band, eluted with 22% ether in

hexane, afforded 5.68 g (26.8 mmol, 47%) of **53** as a clear colorless thick oil after concentration. The spectral data for **53** were: IR (thin film) 3580-3140, 1715, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81 (dd, 1 H, J = 15.6, 7.2 Hz), 5.79 (d, 1 H, J = 15.6 Hz), 4.15 (q, 2 H, J = 6.9 Hz), 3.54 (m, 1 H), 3.37 (m, 1 H), 2.02 (m, 1 H), 1.76 (m, 6 H), 1.30 (m, 4 H), 1.26 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 166.8, 153.0, 120.8, 66.1, 60.3, 43.9, 43.2, 32.4, 28.8, 25.6, 25.4, 14.3; MS (CI, isobutane): *m/e* (%) 213 (M+1, 26), 182 (23), 167 (100), 149 (8), 135 (8), 121 (12), 81 (9), 67 (7), 57 (71); HRMS, *m/e* for $C_{12}H_{20}O_3$: calcd, 212.1412; found, 212.1415.

General Procedure for the Preparation of Methanesulfonate Esters 45, 54, and 79 from Alcohols 44, 53, and 78. The general procedure of Crossland and Servis[42] was followed. To a stirred and cooled (0-5°C) 30-mL methylene chloride solution of 8.7 mmol of the alcohol and 1.32 g (13 mmol) of triethylamine was added 1.20 g (10.4 mmol) of methanesulfonyl chloride dropwise over the course of 10 min. The resulting mixture was stirred for 30 min with continued cooling. The mixture was poured into a 125 mL separatory funnel and extracted with ice water, 1.0 *M* HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the methanesulfonate ester as a light yellow to dark orange oil that was used directly. The physical and spectral properties of the products were the following:

(1*S,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(methanesulfonyloxymethyl)cyclohexane (45)**: 2.22 g (7.66 mmol, 88%); IR (thin film) 1720, 1655, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (dd, 1 H, J = 15.6, 7.2 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 4.00 (m, 2 H), 2.99 (s, 3 H), 2.71 (m, 1 H), 2.10 (m, 1 H), 1.80-1.48 (complex, 6 H), 1.40 (m, 2 H), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.2, 147.7, 122.8, 71.4, 60.3, 39.4, 38.8, 37.1, 29.9, 24.6, 24.2, 21.7, 14.1; MS (CI, isobutane): *m/e* (%) 293 (M+3, 3), 291 (M+1, 39), 245 (100), 195 (41), 165 (19), 149 (17), 148 (18), 121 (71), 120 (42), 93 (22), 91 (16), 81 (23), 79 (35).

(1*R,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(methanesulfonyl-oxymethyl)cyclohexane (54)**: 2.30 g (7.92 mmol, 91%); IR (thin film) 1710, 1645, 1365, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (dd, 1 H, J = 15.6, 6.9 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.16 (q, 2 H, J = 7.2 Hz), 4.09 (m, 1 H), 3.97 (m, 1 H), 2.95 (s, 3 H), 2.04 (m, 1 H), 1.95 (m, 1 H), 1.70 (m, 4 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.21 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 151.0, 121.8, 72.7, 60.4, 42.9, 40.9, 37.1, 32.3, 28.5, 25.2, 25.1, 14.2; MS (CI, isobutane): *m/e* (%) 293 (M+3, 6), 291 (M+1, 100), 247 (4), 245 (77), 194 (26), 165 (21), 148 (31), 121 (92), 107 (12), 93 (16), 79 (21), 67 (12).

1-(2-Methanesulfonyloxyethyl)-1-vinylcyclohexane (79): 1.98 g (8.53 mmol, 98%); IR (thin film) 3060, 1630, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.60 (m, 1 H), 5.08 (m, 1 H), 4.95 (m, 1 H), 4.18 (t, 2 H, J = 7.5 Hz), 2.95 (s, 3 H), 1.76 (t, 2 H, J = 7.5 Hz), 1.56 (m, 2 H), 1.45 (m, 4 H), 1.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 144.7, 114.1, 67.4, 39.2, 38.8, 37.4, 35.7, 26.2, 21.9; HRMS, *m/e* for $C_{11}H_{20}O_3S$: calcd, 232.1133; found, 232.1128.

General Procedure for the Preparation of Alkyl Bromides 46, 55, and 80 from Methanesulfonate Esters 45, 54, and 79. A modification of the procedure reported by Tufariello and coworkers[43] was followed. To a stirred mixture of 3.33 g (38.3 mmol) of anhydrous lithium bromide (LiBr) and 6.86 g (38.3 mmol, 6.7 mL) of hexamethylphosphoramide (HMPA) in 75 mL of dry ether was added dropwise a solution of 7.8 mmol of the methanesulfonate ester in 20 mL of dry ether and the resulting mixture was refluxed with stirring for 12 h. The mixture was cooled to 25°C and washed with 1.0 *M* HCl, water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude bromide product as a light yellow oil which was purified by either vacuum distillation using a Kugelrohr apparatus or by column chromatography on a 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing the concentrations of ether in hexane. The physical and spectral properties of the products were the following:

(1*S,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(bromomethyl)-cyclohexane (46)**: The first and largest band, eluted with 3% ether in hexane, afforded 1.93 g (7.02 mmol, 90%) of **46** as a clear colorless thin oil after concentration. The spectral data for **46** were: IR (thin film) 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (dd, 1 H, J = 15.6, 6.9 Hz), 5.95 (d, 1 H, J = 15.6 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.25 (m, 1 H), 3.15 (m, 1 H), 2.81 (m, 1 H), 1.97 (m, 1 H), 1.80-1.45 (complex, 6 H), 1.38 (m, 2 H), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 147.5, 123.0, 60.3, 42.6, 40.2, 36.7, 30.3, 27.2, 24.9, 21.6, 14.2; MS (CI, isobutane): *m/e* (%) 277 (M+3, 96), 275 (M+1, 100), 195 (21), 149 (13), 121 (20); HRMS, *m/e* for $C_{12}H_{19}O_2{}^{79}Br$: calcd, 274.0568; found, 274.0562; *m/e* for $C_{12}H_{19}O_2{}^{81}Br$: calcd, 276.0548; found, 276.0548.

(1*R,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-(bromomethyl)-cyclohexane (55)**: The first and largest band, eluted with 4% ether in hexane, afforded 1.86 g (67.9 mmol, 87%) of **55** as a clear colorless thin oil after concentration. The spectral data for **55** were: IR (thin film) 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72 (dd, 1 H, J = 15.6, 6.6 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 6.9 Hz), 3.42 (m, 1 H), 3.28 (m, 1 H), 2.13 (m, 2 H), 1.65 (m, 4 H), 1.48 (m, 1 H), 1.29 (t, 3 H, J = 6.9 Hz), 1.23 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 166.6, 151.2, 121.9, 60.3, 44.3, 42.3, 39.8, 32.1, 30.2, 25.5, 25.2, 14.3; MS (CI, isobutane): *m/e* (%) 277 (M+3, 97), 275 (M+1, 100), 231 (15), 229 (17), 195 (39), 181 (26), 149 (35), 121 (37), 107 (16), 95 (25); HRMS, *m/e* for $C_{12}H_{19}O_2{}^{79}Br$: calcd, 274.0568; found, 274.0568; *m/e* for $C_{12}H_{19}O_2{}^{81}Br$: calcd, 276.0548; found, 276.0548.

1-(2-Bromoethyl)-1-vinylcyclohexane (80): Vacuum distillation of the crude product oil yielded 1.27 g (58.5 mmol, 75%) of **80** as a clear colorless thin oil, bp 60-63°C (1.0 mm Hg). The spectral data for **80** were: IR (thin film) 3060, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.59 (m, 1 H), 5.15 (m, 1 H), 4.97 (m, 1 H), 3.30 (m, 2 H), 1.91 (m, 2 H), 1.54 (m, 2 H), 1.46 (m, 5 H), 1.36 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.8,

113.9, 44.4, 41.0, 35.4, 29.2, 26.3, 22.0; HRMS, *m/e* for $C_{10}H_{17}{}^{79}Br$: calcd, 216.0513; found, 216.0512; *m/e* for $C_{10}H_{17}{}^{81}Br$: calcd, 218.0493; found, 218.0486.

General Procedure for the Preparation of the Ethyl Esters 60 and 61 of Acids 58 and 59. The general procedure of Munche-Peterson[45] was followed. In a 500-mL round-bottomed flask equipped with a Dean-Stark trap and reflux condenser, a solution of 200 mmol of the carboxylic acid, 44 mL of absolute ethanol, and 1 mL of concentrated sulfuric acid in 100 mL of dry benzene were refluxed with stirring until the evolution of water had ceased (*ca.* 18 h). The mixture was cooled to 25°C and poured into 50 mL of saturated aqueous $NaHCO_3$. The resulting organic layer was separated and washed with 50 mL of water, 50 mL of saturated aqueous $NaHCO_3$, 50 mL of water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude ester product as a clear light yellow oil which was purified by distillation at aspirator pressure. The physical and spectral properties of the products were the following:

Ethyl Cyclopentanecarboxylate (60): 22.4 g (158 mmol, 79%); bp 68-70°C (20 mm Hg); IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7.2 Hz), 2.71 (m, 1 H), 1.95-1.55 (complex, 8 H), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 176.8, 60.1, 43.8, 30.0, 25.8, 14.2; HRMS, *m/e* for $C_8H_{14}O_2$: calcd, 142.0994; found, 142.0993.

Ethyl Cyclohexanecarboxylate (61): 25.0 g (160 mmol, 80%); bp 76-78°C (20 mm Hg); IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 6.9 Hz), 2.28 (m, 1 H), 1.90 (m, 2 H), 1.75 (m, 2 H), 1.66 (m, 1 H), 1.44 (m, 2 H), 1.28 (m, 3 H), 1.25 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.1, 59.9, 43.2, 29.0, 25.7, 25.4, 14.2; HRMS, *m/e* for $C_9H_{16}O_2$: calcd, 156.1150; found, 156.1153.

General Procedure for the Alkylation of Esters 60 and 61 (62 and 63). The general procedure of Williams and Sirvio[46] was followed. To a stirred 25-mL THF solution of 15.6 mL of 1.6 *M* *n*-butyllithium (25 mmol) in hexanes at 0-5°C was

added 3.24 g (32 mmol, 4.49 mL) of dry diisopropylamine dropwise over the course of 5 min. The resulting solution was stirred at 0-5°C for 15 min. The solution was then cooled to -78°C and 22.0 mmol of the ester was added dropwise with continued stirring. Following 30 min of stirring at -78°C, a solution of 2.91 g (24 mmol) of allyl bromide in 4 mL of HMPA was added dropwise. After 10 min of stirring at -78°C, the resulting mixture was warmed to 25°C and stirred for 9 h. The mixture was then cautiously treated with 5 mL of saturated aqueous NH_4Cl and the THF was removed by rotary evaporation to yield a dark yellow residue. The isolated residue was treated with 50 mL of water and the resulting aqueous mixture was extracted twice with ether. The combined ether extracts were washed with water, 0.5 *M* aqueous HCl, water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a clear light yellow oil which was purified by distillation at aspirator pressure. The physical and spectral properties of the products were the following:

Ethyl 1-(2-Propenyl)cyclopentanecarboxylate (62): 3.12 g (17.1 mmol, 78%); bp 98-100°C (20 mm Hg); IR (thin film) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.71 (m, 1 H), 5.02 (m, 2 H), 4.12 (q, 2 H, J = 7.2 Hz), 2.36 (d, 2 H),2.08 (m, 2 H), 1.70-1.46 (complex, 6 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3, 134.9, 117.2, 60.3, 53.5, 42.9, 35.5, 25.0, 14.2; HRMS, *m/e* for $C_{11}H_{18}O_2$: calcd, 182.1307; found, 182.1305.

Ethyl 1-(2-Propenyl)cyclohexanecarboxylate (63): 3.67 g (18.7 mmol, 85%); bp 108-110°C (20 mm Hg); IR (thin film) 1735, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.69 (m, 1 H), 5.00 (m, 2 H), 4.14 (q, 2 H, J = 6.9 Hz), 2.23 (d, 2 H), 2.05 (m, 2 H), 1.55 (m, 3 H), 1.43-1.17 (complex, 5 H), 1.25 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 133.7, 117.4, 60.0, 47.0, 44.6, 33.7, 25.8, 23.1, 14.3; HRMS, *m/e* for $C_{12}H_{20}O_2$: calcd, 196.1463; found, 196.1461.

General Procedure for the Reduction of Esters 62 and 63 (64 and 65). To a stirred slurry of 2.5 g (66 mmol) of $LiAlH_4$ in 150 mL of dry THF was added

a solution of 66 mmol of the ester in 50 mL of dry THF dropwise over the course of 5 min. The resulting mixture was refluxed with stirring for 2 h. The mixture was then cooled (0-5°C) and quenched cautiously with 3 mL of water, 10 mL of 5% aqueous NaOH and 5 mL of water. The insoluble aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite® in a large frit and washed with several portions of hot THF. The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude alcohol product as a clear light yellow oil which was purified by vacuum distillation. The physical and spectral properties of the products were the following:

1-(Hydroxymethyl)-1-(2-propenyl)cyclopentane (64): 7.40 g (52.9 mmol, 80%); bp 68-69°C (1.0 mm Hg); IR (thin film) 3600-3140, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (m, 1 H), 5.07 (m, 2 H), 3.40 (s, 2 H), 2.16 (d, 2 H), 1.60 (m, 5 H), 1.43 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 136.2, 116.9, 69.0, 47.2, 41.9, 34.1, 25.2; HRMS, *m/e* for $C_9H_{16}O$: calcd, 140.1201; found, 140.1204.

1-(Hydroxymethyl)-1-(2-propenyl)cyclohexane (65): 7.58 g (49.2 mmol, 73%); bp 76-78°C (1.0 mm Hg); IR (thin film) 3560-3120, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (m, 1 H), 5.07 (m, 2 H), 3.41 (s, 2 H), 2.12 (d, 2 H), 1.66 (bs, 1 H), 1.44 (m, 6 H), 1.33 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 135.3, 116.9, 68.6, 39.8, 37.7, 32.2, 26.3, 21.4; HRMS, *m/e* for $C_{10}H_{18}O$: calcd, 154.1358; found, 154.1355.

General Procedure for the Conversion of Alcohols 64 and 65 to the Corresponding Chlorides (66 and 67). The general procedure of Lee and Nolen[47] was followed. An 80-mL carbon tetrachloride solution of 43 mmol of the alcohol and 12.4 g (47 mmol) of triphenylphosphine was refluxed with stirring for 12 h. The reaction mixture was cooled to 25°C and the carbon tetrachloride was removed by rotary evaporation under vacuum. The resulting white solid was subjected to flash vacuum chromatography through a 20 cm x 12 cm plug of silica gel in a large frit using 95:5 hexane/ether. The collected eluent was concentrated to afford the crude chloride product

as a light yellow oil which was purified by distillation at aspirator pressure. The physical and spectral properties of the products were the following:

1-(Chloromethyl)-1-(2-propenyl)cyclopentane (66): 4.91 g (31.0 mmol, 72%); bp 75-78°C (20 mm Hg); IR (thin film) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (m, 1 H), 5.09 (m, 2 H), 3.42 (s, 2 H), 2.23 (d, 2 H), 1.68 (m, 4 H), 1.51 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 134.7, 117.9, 52.8, 42.0, 41.4, 35.4, 25.0; HRMS, *m/e* for $C_9H_{15}{}^{35}Cl$: calcd, 158.0862; found, 158.0859; *m/e* for $C_9H_{15}{}^{37}Cl$: calcd, 160.0833; found, 160.0834.

1-(Chloromethyl)-1-(2-propenyl)cyclohexane (67): 5.64 g (32.7 mmol, 76%); bp 82-84°C (20 mm Hg); IR (thin film) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.10 (m, 2 H), 3.52 (s, 2 H), 2.13 (d, 2 H), 1.47 (m, 6 H), 1.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 134.7, 117.0, 43.9, 39.6, 37.3, 32.3, 26.5, 21.0; HRMS, *m/e* for $C_{10}H_{17}{}^{35}Cl$: calcd, 172.1019; found, 172.1018; *m/e* for $C_{10}H_{17}{}^{37}Cl$: calcd, 174.0989; found, 174.0987.

General Procedure for the Ozonolysis of Olefins 66, 67, and 80 to the Corresponding Aldehydes (68, 69, and 81). A 50-mL methanol solution of 24 mmol of the olefin at -78°C was treated with ozone for 30 min. The solution was then treated with 4 mL of dimethyl sulfide and 1 mL of glacial acetic acid with continued cooling. The mixture was concentrated *in vacuo* and the isolated residue was dissolved in 100 mL of ether. The resulting ether solution was washed with 0.5 *M* aqueous HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield the crude aldehyde product as a clear liquid which was used directly. The physical and spectral properties of the products were the following:

1-(Chloromethyl)-1-(formylmethyl)cyclopentane (68): 3.82 g (23.8 mmol, 99%); IR (thin film) 2740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.78 (bs, 1 H), 3.56 (s, 2 H), 2.42 (s, 2 H), 1.70 (m, 4 H), 1.52 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 201.7, 47.9, 43.2, 42.6, 32.8, 26.5; HRMS, *m/e* for $C_8H_{13}O^{35}Cl$: calcd, 160.0655; found,

160.0658; *m/e* for $C_8H_{13}O^{37}Cl$: calcd, 162.0625; found, 162.0627.

1-(Chloromethyl)-1-(formylmethyl)cyclohexane (69): 4.17 g (23.9 mmol, 99%); IR (thin film) 2740, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (bs, 1 H), 3.59 (s, 2 H), 2.41 (s, 2 H), 1.46 (m, 6 H), 1.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 202.0, 46.3, 39.7, 38.1, 31.8, 27.3, 21.1; HRMS, *m/e* for $C_9H_{15}O^{35}Cl$: calcd, 174.0811; found, 174.0815; *m/e* for $C_9H_{15}O^{37}Cl$: calcd, 176.0782; found, 176.0786.

1-(2-Bromoethyl)cyclohexanecarboxaldehyde (81): 4.31 g (19.7 mmol, 82%); IR (thin film) 2725, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.87 (bs, 1 H), 3.46 (t, 2 H, J = 6.9 Hz), 2.27 (t, 2 H, J = 6.9 Hz), 1.43 (m, 6 H), 1.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 201.9, 44.8, 38.5, 34.7, 31.0, 27.5, 21.2; HRMS, *m/e* for $C_9H_{15}O^{79}Br$: calcd, 218.0306; found, 218.0312; *m/e* for $C_9H_{15}O^{81}Br$: calcd, 220.0286; found, 220.0283.

General Wittig Olefination Procedure for the Conversion of Aldehydes 68, 69, and 81 to the Corresponding Ethyl Enoate Esters (70, 71, and 82). A 100-mL benzene solution of 36.7 mmol of the aldehyde and 12.8 g (36.7 mmol) of ethyl (triphenylphosphoranylidene)acetate was refluxed for 16 h with stirring. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light yellow solid residue. The residue was subjected to flash vacuum chromatography[62] through a 20 cm x 12 cm plug of silica gel in a large frit using 90:10 hexane/ether. Concentration of the collected eluent afforded the crude enoate ester products as clear light yellow oils which were purified by column chromatography on a 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing the concentrations of ether in hexane. The physical and spectral properties of the products were the following:

1-(Chloromethyl)-1-((*E*)-3-ethoxycarbonyl-2-propenyl)cyclopentane (70): The first and largest band, eluted with 4% ether in hexane, afforded 6.08 g (26.4 mmol, 72%) of **70** as a clear colorless thin oil after concentration. The spectral data for **70** were: IR (thin film) 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (dt, 1 H, J = 15.6, 7.8 Hz), 5.92 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 6.9 Hz), 3.41 (s, 2 H), 2.37 (d,

2 H, J = 7.8 Hz), 1.72-1.50 (complex, 8 H), 1.30 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.1, 124.3, 60.2, 52.4, 47.5, 39.7, 35.6, 24.9, 14.2; MS (CI, isobutane): *m/e* (%) 232 (M+2, 15), 230 (44), 185 (11), 121 (17), 114 (100), 97 (15), 95 (15), 86 (37), 81 (66), 67 (22).

1-(Chloromethyl)-1-((*E*)-3-ethoxycarbonyl-2-propenyl)cyclohexane (71): The first and largest band, eluted with 4% ether in hexane, yielded 6.65 g (27.2 mmol, 74%) of **71** as a clear colorless oil after concentration. The spectral data for **71** were: IR (thin film) 1725, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.91 (dt, 1 H, J = 15.3, 8.1 Hz), 5.91 (d, 1 H, J = 15.3 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.43 (s, 2 H), 2.31 (d, 2 H, J = 8.1 Hz), 1.57-1.37 (complex, 10 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13} C NMR ($CDCl_3$) δ 166.2, 144.2, 124.4, 60.1, 51.9, 38.2, 37.8, 33.4, 25.8, 21.3, 14.2; MS (CI, isobutane): *m/e* (%) 246 (M+2, 13), 244 (39), 114 (100), 95 (47), 86 (26).

1-(2-Bromoethyl)-1-((*E*)-ethoxycarbonylethenyl)cyclohexane (82): The first and largest band, eluted with 4% ether in hexane, afforded 7.54 g (26.1 mmol, 71%) of **82** as a clear colorless oil after concentration. The spectral data for **82** were: IR (thin film) 1715, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.77 (d, 1 H, J = 16.2 Hz), 5.76 (d, 1 H, J = 16.2 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.23 (m, 2 H), 1.98 (m, 2 H), 1.59 (m, 2 H), 1.41 (m, 8 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 154.8, 120.8, 60.4, 43.9, 41.3, 35.2, 28.1, 26.0, 22.0, 14.3; MS (EI/DP): *m/e* (%) 290 (M+2, 2), 288 (2), 245 (11), 243 (12), 209 (12), 182 (15), 181 (100), 163 (10), 135 (40), 121 (10), 107 (37), 93 (15), 79 (27), 67 (30), 55 (15); HRMS, *m/e* for $C_{13}H_{21}O_2{}^{79}Br$: calcd, 288.0725; found, 288.0728; *m/e* for $C_{13}H_{21}O_2{}^{81}Br$: calcd, 290.0704; found, 290.0698.

Methyl Cyclohexylideneacetate (75). The general procedure of Wadsworth and Emmons[49] was used. To a stirred and cooled (0-5°C) slurry of 2.4 g (100 mmol) of sodium hydride in 50 mL of dry benzene was added 18.2 g (100 mmol) of trimethyl phosphonoacetate in a dropwise manner over the course of 45 min and the resulting

mixture was stirred at 25°C for 1 h. The mixture was cooled (0-5°C) and 9.8 g (100 mmol) of cyclohexanone (**74**) was slowly added over 30 min with vigorous stirring. The resulting mixture was then refluxed for 12 h and cooled to 25°C. The mixture was concentrated *in vacuo* to yield a thick oily residue and 100 mL of water was added. The resulting aqueous mixture was extracted twice with ether. The combined ether extracts were washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a clear light yellow oil which was purified by vacuum distillation to afford 13.71 g (89 mmol, 89%) of **75** as a clear colorless thin oil, bp 53-56°C (0.5 mm Hg). The spectral data for **75** were: IR (thin film) 1725, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (s, 1 H), 3.65 (s, 3 H), 2.81 (m, 2 H), 2.17 (m, 2 H), 1.60 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.2, 163.9, 112.6, 50.8, 38.0, 29.8, 28.6, 27.8, 26.2; HRMS, *m/e* for $C_9H_{14}O_2$: calcd, 154.0994; found, 154.0996.

Cyclohexylidenemethanol (76). The general procedure of Angus and Johnson[50] was followed. To a stirred and cooled (0-5°C) slurry of 3.79 g (100 mmol) of $LiAlH_4$ in 250 mL of dry ether was added a solution of 15.4 g (100 mmol) of **75** in 100 mL of dry ether dropwise over the course of 30 min. The resulting mixture was stirred with continued cooling for 2 h. The mixture was then quenched cautiously with 4 mL of water, 12 mL of 5% aqueous NaOH and 4 mL of water with vigorous stirring and continued cooling. The insoluble aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite® in a large frit and washed with several portions of hot THF. The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude alcohol as a clear colorless oil which was purified by vacuum distillation to afford 11.2 g (89 mmol, 89%) of **76** as a clear colorless liquid, bp 47-49°C (0.5 mm Hg). The spectral data for **76** were: IR (thin film) 3520-3100, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (t, 1 H, J = 6.6 Hz), 4.09 (d, 2 H, J = 6.6 Hz), 2.15 (m, 2 H), 2.04 (m, 2 H), 1.98 (bs, 1 H), 1.54 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 144.1, 120.4, 58.4, 37.0, 28.8, 28.4, 27.8, 26.7; MS (EI/DP): *m/e* (%) 126 (19), 108 (100), 93 (82), 83

(82), 79 (94), 70 (30), 67 (96), 55 (40); HRMS, *m/e* for $C_8H_{14}O$: calcd, 126.1045; found, 126.1038.

1-(Carboxymethyl)-1-vinylcyclohexane (77). A solution of 5.04 g (40.0 mmol) of **56**, 19.5 g (120 mmol) of triethyl orthoacetate and 2 drops of propanoic acid were slowly heated to 140-150°C with stirring in a 50-mL round-bottomed flask equipped with a short-path distillation apparatus until the evolution of ethanol had ceased (*ca.* 30 min). The resulting mixture was heated at this temperature range with stirring for an additional 2 h. The mixture was then cooled and the excess orthoester was removed by distillation at aspirator pressure. To the remaining oil was added a solution of 11.22 g (200 mmol) of KOH in 40 mL of water and the resulting mixture was refluxed with stirring for 16 h. The mixture was cooled to 25°C and extracted twice with ether. The isolated aqueous phase was then cooled (0-5°C) and carefully acidified with 6 *M* aqueous HCl to a pH of *ca.* 3. The acidified mixture was extracted twice with ether. The combined ether extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield 4.86 g (28.9 mmol, 72%) of **77** as a white solid, mp 52-54°C, which was used without further purification. The spectral data for **77** were: IR ($CHCl_3$) 3515-2960, 1720, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.40 (bs, 1 H), 5.80 (m, 1 H), 5.08 (m, 2 H), 2.35 (s, 2 H), 1.67 (m, 2 H), 1.48 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 178.4, 144.5, 113.6, 45.7, 39.1, 35.6, 26.1, 22.1; HRMS, *m/e* for $C_{10}H_{16}O_2$: calcd, 168.1150; found, 168.1152.

1-(2-Hydroxyethyl)-1-vinylcyclohexane (78). To a stirred slurry of 0.75 g (19.8 mmol) of $LiAlH_4$ in 70 mL of dry THF at 23°C was added a solution of 2.78 g (16.5 mmol) of **77** in 25 mL of dry THF over the course of 15 min and the resulting mixture was heated at reflux for 3 h. The reaction mixture was then cooled (0-5°C) and 10 mL of a freshly prepared solution of saturated aqueous Na_2SO_4 was cautiously added dropwise with continued stirring and cooling. The insoluable aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite® and were washed

with several portions of hot THF. The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield a clear light yellow oil which was purified by vacuum distillation to afford 2.18 g (14.2 mmol, 86%) of **78** as a colorless oil, bp 68-69°C (0.5 mm Hg). The spectral data for **78** were: IR (thin film) 3550-3120, 3060, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (m, 1 H), 5.02 (m, 2 H), 3.61 (t, 2 H, J = 7.2 Hz), 1.75 (bs, 1 H), 1.60 (t, 2 H, J = 7.2 Hz), 1.56 (m, 1 H), 1.44 (m, 6 H), 1.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.6, 113.0, 59.3, 43.5, 38.8, 35.8, 26.4, 22.0; HRMS, *m/e* for $C_{10}H_{18}O$: calcd, 154.1358; found, 154.1356.

General Annulation Procedure for the Preparation of Dihydroisoindole Products 83, 84, and 85. A 20-mL methanol solution of 1.00 g (3.92 mmol) of **33**, 3.92 mmol of the primary amine and 0.44 g (4.35 mmol) of triethylamine was stirred at 25°C for 24 h. The mixture was concentrated *in vacuo* to afford a thick golden residue which was treated with 50 mL of water and extracted twice with ether. The combined ether extracts were washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield the crude dihydroisoindole product as a light yellow oil which was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing concentrations of ether in hexane. The physical and spectral properties of the products were the following:

Methyl (±)-2-(2-Phenylethyl)-2,3-dihydro-1*H*-isoindole-1-acetate (83): The third and largest band, eluted with 9% ether in hexane, afforded 820 mg (2.78 mmol, 71%) of **83** as a colorless oil after concentration. The spectral data for **83** were: IR (thin film) 3020, 1735, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (m, 9 H), 4.37 (m, 2 H), 3.79 (m, 2 H), 3.69 (s, 3 H), 3.13 (m, 1 H), 2.85 (m, 2 H), 2.70 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 142.4, 140.2, 139.2, 128.6, 128.3, 127.2, 126.9, 126.0, 122.2, 122.1, 65.6, 58.1, 56.0, 51.6, 40.2, 35.3; MS (EI/DP): *m/e* (%) 295 (2), 223 (6), 222 (34), 205 (14), 204 (100), 162 (18), 115 (13), 105 (31), 104 (11), 91 (10), 77 (9).

Methyl (±)-2-(Phenylmethyl)-2,3-dihydro-1*H*-isoindole-1-acetate (84): The third and largest band, eluted with 9% ether in hexane, yielded 760 mg (2.70 mmol, 69%) of **84** as a clear colorless oil after concentration. The spectral data for **84** were: IR (thin film) 3020, 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39-7.10 (complex, 9 H), 4.49 (t, 1 H, J = 5.4 Hz), 4.17 (d, 1 H, J = 13.2 Hz), 4.08 (d, 1 H, J = 13.2 Hz), 3.70 (s, 3 H), 3.64 (m, 2 H), 2.81 (d, 2 H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 142.2, 139.3, 128.6, 128.3, 127.2, 127.0, 126.9, 122.3, 122.2 (2), 65.5, 58.4, 58.0, 51.6, 40.2; HRMS, *m/e* for $C_{18}H_{19}NO_2$: calcd, 281.1416; found, 281.1415. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.83; H, 6.81. Found: C, 76.51; H, 6.79.

Methyl (±)-2-(Cyclohexyl)-2,3-dihydro-1*H*-isoindole-1-acetate (85): The third and largest band, eluted with 10% ether in hexane, afforded 660 mg (2.42 mmol, 62%) of **85** as a colorless oil after concentration. The spectral data for **85** were: IR (thin film) 3020, 1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (m, 4 H), 4.73 (dd, 1 H, J = 8.1, 5.1 Hz), 4.11 (d, 1 H, J = 13.5 Hz), 4.03 (d, 1 H, J = 13.5 Hz), 3.72 (s, 3 H), 2.78 (dd, 1 H, J = 15.2, 5.1 Hz), 2.64 (m, 1 H), 2.58 (dd, 1 H, J = 15.2, 8.1 Hz), 1.83 (m, 4 H), 1.65 (m, 1 H), 1.42-1.24 (complex, 5H); ^{13}C NMR ($CDCl_3$) δ 172.7, 142.9, 139.6, 127.0, 126.7, 122.2 (2), 61.5, 58.8, 52.8, 51.5, 40.3, 32.4, 27.6, 26.2, 26.0, 25.5; MS (EI/DP): *m/e* (%) 273 (4), 230 (6), 200 (100), 190 (8), 158 (6), 144 (11), 130 (14), 118 (46), 91 (11), 55 (11).

Ethyl (*E*)-2-Vinylcinnamate (93). A 10-mL ethanol solution of 1.65 g (5.0 mmol) of **38**, 536 mg (5.0 mmol) of benzylamine and 557 mg (5.5 mmol) of triethylamine were refluxed with stirring for 24 h. The mixture was cooled to 25°C and concentrated *in vacuo* to yield a light yellow residue which was treated with 50 mL of water. The resulting aqueous mixture was extracted twice with ether and the combined ether extracts were washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil that was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with

increasing concentrations of ether in hexane. The first and major band collected, eluted with 97:3 hexane/ether, yielded 900 mg (4.5 mmol, 90%) of **93** as a colorless light oil after concentration. Further elutions with up to 50:50 hexane/ether yielded none of the desired annulation product. The spectral data for **93** were: IR (thin film) 1710, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (d, 1 H, J = 16.2 Hz), 7.50 (m, 2 H), 7.32 (m, 2 H), 7.07 (m, 1 H), 6.35 (d, 1 H, J = 16.2 Hz), 5.63 (m, 1 H), 5.42 (m, 1 H), 4.27 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.8, 142.3, 138.0, 134.2, 132.5, 130.0, 127.9, 127.0 (2), 120.3, 118.0, 60.5, 14.4; MS (CI, isobutane): *m/e* (%) 203 (M+1, 64), 159 (18), 157 (69), 155 (16), 129 (100), 117 (10), 102 (14); HRMS, *m/e* for $C_{13}H_{14}O_2$: calcd, 202.0988; found, 202.0974.

Ethyl (*E*)-2-(2-Phthalimidoethyl)cinnamate (94). The general procedure of Baker and Sifniades[51] was followed. To a stirred solution of 1.41 g (5.0 mmol) of **37** in 15 mL of dry dimethylformamide (DMF) was added 1.02 g (5.5 mmol) of neat potassium phthalimide in small portions while maintaining the reaction temperature below 50°C. The resulting mixture was stirred at 25°C for 24 h. To the mixture was added 50 mL of chloroform and the isolated organic layer was washed with two 75 mL portions of water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a light yellow solid residue which was recrystallized twice from methanol to yield 1.53 g (4.4 mmol, 88%) of **94** as a fine white solid, mp 112-113°C. The spectral data for **94** were: IR ($CHCl_3$) 1775, 1725, 1710, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, 1 H, J = 15.6 Hz), 7.79 (m, 2 H), 7.68 (m, 2 H), 7.54 (m, 1 H), 7.24 (m, 3 H), 6.29 (d, 1 H, J = 15.6 Hz), 4.25 (q, 2 H, J = 7.2 Hz), 3.88 (t, 2 H, J = 7.8 Hz), 3.12 (t, 2 H, J = 7.8 Hz), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 168.0, 166.6, 141.3, 137.6, 133.9, 133.7, 132.0, 130.5, 130.2, 127.4, 126.7, 123.2, 120.3, 60.5, 38.8, 32.0, 14.3; MS(EI/DP): *m/e* (%) 349 (2), 303 (30), 275 (3), 202 (8), 160 (100), 129 (37), 115 (13), 104 (6); HRMS, *m/e* for $C_{21}H_{19}NO_4$: calcd, 349.1314; found, 349.1319.

Ethyl (±)-1,2,3,4-Tetrahydroisoquinoline-1-acetate (96). The general procedure of Boeckman and co-workers[19] was followed. A solution of 1.00 g (2.87 mmol) of **94** and 129 mg (4.02 mmol) of hydrazine in 10 mL of absolute ethanol was refluxed with stirring for 6 h. The resulting mixture was cooled to 25°C and concentrated *in vacuo* to afford a solid yellow residue which was dissolved in ether. The organic layer was washed with 1 *M* aqueous NaOH and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil which was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing concentrations of ether in hexane. The first and major band collected, eluted with 70:30 hexane/ether, yielded 453 mg (2.07 mmol, 72%) of **96** as a clear colorless oil after concentration. The spectral data for **96** were: IR (thin film) 3340, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (m, 4 H), 4.48 (m, 1 H), 4.18 (q, 2 H, J = 6.9 Hz), 3.21 (m, 1 H), 3.03 (m, 1 H), 2.81 (m, 4 H), 2.64 (bs, 1 H), 1.26 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 137.4, 135.4, 129.5, 126.4, 126.0, 125.9, 60.6 (CH_2), 52.7 (CH), 41.3 (CH_2), 40.7 (CH_2), 29.7 (CH_2), 14.2 (CH_3); MS (EI/DP): *m/e* (%) 219 (9), 204 (8), 190 (4), 172 (5), 133 (11), 132 (100), 130 (11), 117 (8), 77 (3).

General Annulation Procedure for the Preparation of Monocyclic Nitrogen Products 86 and 87. A 15-mL methanol solution of 5.6 mmol of the iodoester (**27** or **28**), 600 mg (5.6 mmol) of benzylamine and 620 mg (6.2 mmol) of triethylamine was refluxed with stirring for 36 h. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light yellow oily residue which was treated with 20 mL of water and extracted twice with ether. The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield the crude annulation product as a clear yellow oil which was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing concentrations of ether in hexane. The physical and spectral properties of the products were the following:

Methyl (±)-1-(Phenylmethyl)-2-pyrrolidineacetate (86): The third and largest band, eluted with 15% ether in hexane, afforded 820 mg (3.53 mmol, 63%) of **86** as a clear colorless oil after concentration. The spectral data for **86** were: IR (thin film) 1740, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 3.97 (d, 1 H, J = 12.9 Hz), 3.67 (s, 3 H), 3.28 (d, 1 H, J = 12.9 Hz), 2.89 (m, 2 H), 2.67 (dd, 1 H, J = 14.7, 7.2 Hz), 2.36 (dd, 1 H, J = 14.7, 7.8 Hz), 2.18 (m, 1 H), 2.05 (m, 1 H), 1.67 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 139.4, 128.7, 128.2, 126.8, 60.7, 58.6, 53.9, 51.4, 39.6, 30.9, 22.1; MS (EI/DP): *m/e* (%) 233 (5), 161 (11), 160 (100), 91 (94), 65 (10).

Methyl (±)-1-(Phenylmethyl)-2-piperidineacetate (87): The third and largest band, eluted with 14% ether in hexane, afforded 810 mg (3.28 mmol, 59%) of **87** as a clear colorless oil after concentration. The spectral data for **87** were: IR (thin film) 1735, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 3.80 (d, 1 H, J = 13.5 Hz), 3.67 (s, 3 H), 3.35 (d, 1 H, J = 13.5 Hz), 2.97 (m, 1 H), 2.72 (dd, 1 H, J = 14.7, 8.1 Hz), 2.62 (m, 1 H), 2.45 (dd, 1 H, J = 14.7, 7.5 Hz), 2.17 (m, 1 H), 1.74 (m, 1 H), 1.61 (m, 1 H), 1.47 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 139.5, 128.7, 128.1, 126.7, 58.5, 57.5, 51.5, 50.1, 36.0, 30.9, 25.1, 22.3; MS (EI/DP): *m/e* (%) 247 (4), 175 (13), 174 (100), 91 (47).

Attempted Spiroannulation of Enoate Esters 70 and 71 Using the Conditions Established. A 15-mL methanol solution of 5.6 mmol of the chloro ester, 600 mg (5.6 mmol) of benzylamine and 620 mg (6.2 mmol) of triethylamine was refluxed with stirring and periodic monitoring of the reaction mixture by TLC. At the end of 120 h of reflux, no annulation product was detected and the reaction was terminated. The bromide analog of **70** also showed a similar lack of reactivity with a >80% recovery of starting material at the end of the heterocyclization attempt using these reaction conditions.

(±)-*N*-(Phenylmethyl)-1-(ethoxycarbonylmethyl)-2-azaspiro[4.5]-decane (88). A 15-mL ethanol solution of 2.25 g (7.8 mmol) of **82**, 840 mg (7.8 mmol) of benzylamine and 870 mg (8.7 mmol) of triethylamine was refluxed with stirring

for 48 h. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a dark yellow oily residue which was treated with 20 mL of water and extracted twice with ether The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a clear yellow oil which was purified by column chromatography on an 80 cm x 2.5 cm slurry packed silica gel column eluted with increasing concentrations of ether in hexane. The third and largest band collected, eluted with 86:14 hexane/ether, afforded 1.68 g (5.34 mmol, 68%) of **88** as a clear light yellow oil after concentration. The spectral data for **88** were: IR (thin film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.14 (q, 2 H, J = 7.2 Hz), 3.98 (d, 1 H, J = 13.2 Hz), 3.32 (d, 1 H, J = 13.2 Hz), 2.82 (m, 2 H), 2.49 (dd, 1 H, J = 15.3, 5.1 Hz), 2.39 (dd, 1 H, J = 15.3, 9.3 Hz), 2.21 (dd, 1 H, J = 9.3, 5.1 Hz), 1.53 (m, 5 H), 1.28 (m, 7 H), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 173.5, 140.2, 128.5, 128.1, 126.6, 70.4, 60.3, 59.9, 51.3, 44.5, 36.4 (2), 33.7, 33.1, 26.4, 23.3, 22.9, 14.2; MS (EI/DP): *m/e* (%) 315 (3), 251 (4), 229 (19), 228 (100), 223 (8), 149 (4), 128 (11), 91 (30); HRMS, *m/e* for $C_{20}H_{29}NO_2$: calcd, 315.2198; found, 315.2196. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.14; H, 9.27. Found: C, 76.44; H, 9.39.

(1*R,3a*S**,7a*S**)-(±)-*N*-(Phenylmethyl)-1-(ethoxycarbonylmethyl)-2, 3, 3a, 4, 5, 6, 7, 7a-octahydro-1*H*-isoindole (89) and (1*S**,3a*S**,7a*S**)-(±)-*N*-(Phenylmethyl)-1-(ethoxycarbonylmethyl)-2, 3, 3a, 4, 5, 6, 7, 7a-octahydro-1*H*-isoindole (90).** A 5-mL ethanol solution of 355 mg (1.29 mmol) of **46**, 138 mg (1.29 mmol) of benzylamine and 144 mg (1.42 mmol) of triethylamine was refluxed with stirring for 120 h. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light yellow residue which was treated with 20 mL of water and extracted twice with ether. The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a clear yellow oil which was purified by PTLC on two

20 cm x 20 cm silica gel PTLC plates eluted with increasing concentrations of ether in hexane. The elution sequence used was: 99:1 hexane/ether (2x), 95:5 hexane/ether (2x), 90:10 hexane/ether (2x) and 85:15 hexane/ether (1x). The third band afforded 19 mg (0.064 mmol, 5%) of **90** as a clear colorless oil after extraction and concentration. The spectral data for **90** were: IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 4.13 (q, 2 H, J = 7.6 Hz), 3.92 (d, 1 H, J = 13.8 Hz), 3.41 (d, 1 H, J = 13.8 Hz), 3.21 (m, 1 H), 2.92 (m, 1 H), 2.49 (m, 2 H), 2.31 (m, 2 H), 2.02 (m, 1 H), 1.71 (m, 1 H), 1.63-1.12 (complex, 7 H), 1.25 (t, 3 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 140.7, 128.3, 128.1, 126.6, 65.3 (CH), 60.2 (CH_2), 58.7 (CH_2), 54.8 (CH_2), 41.0 (CH), 35.4 (CH), 35.4 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 22.9 (CH_2), 20.9 (CH_2), 14.2 (CH_3); HRMS, *m/e* for $C_{19}H_{27}NO_2$: calcd, 301.2036; found, 301.2036. The fourth and largest band yielded 268 mg (0.891 mmol, 69%) of **89** as a clear colorless oil after extraction and concentration. The spectral data for **89** were: IR (thin film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 4.12 (q, 2 H, J = 7.2 Hz), 4.02 (d, 1 H, J = 13.2 Hz), 3.59 (d, 1 H, J = 13.2 Hz), 2.98 (m, 1 H), 2.80 (m, 1 H), 2.45 (m, 2 H), 2.30 (m, 2 H), 1.82 (m, 1 H), 1.58 (m, 4 H), 1.35 (m, 4 H), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 140.2, 128.6, 128.1, 126.7, 66.7 (CH), 60.6 (CH_2), 60.2 (CH_2), 56.0 (CH_2), 43.7 (CH), 41.3 (CH_2), 35.8 (CH), 28.4 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 14.3 (CH_3); HRMS, *m/e* for $C_{19}H_{27}NO_2$: calcd, 301.2036; found, 301.2035. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.70; H, 9.03. Found: C, 75.94; H, 9.18.

(1*R,3a*S**,7a*R**)-(±)-*N*-(Phenylmethyl)-1-(ethoxycarbonylmethyl)-2, 3, 3a, 4, 5, 6, 7, 7a-octahydro-1*H*-isoindole (91) and (1*S**,3a*S**,7a*R**)-(±)-*N*-(Phenylmethyl)-1-(ethoxycarbonylmethyl)-2, 3, 3a, 4, 5, 6, 7, 7a-octahydro-1*H*-isoindole (92).** A 5-mL ethanol solution of 355 mg (1.29 mmol) of **55**, 138 mg (1.29 mmol) of benzylamine and 144 mg (1.42 mmol) of triethylamine was refluxed with stirring for 96 h. The mixture was cooled to 25°C and concentrated *in vacuo* to afford a light yellow residue which was treated with 20 mL of water and

extracted twice with ether. The combined ether extracts were washed with water, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a clear light yellow oil which was purified by PTLC on two 20 cm x 20 cm silica gel PTLC plates eluted with increasing concentrations of ether in hexane. The elution sequence used was: 99:1 hexane/ether (2x), 95:5 hexane/ether (2x), 90:10 hexane/ether (4x) and 85:15 hexane/ether (1x). The third band afforded 49 mg (0.163 mmol, 13%) of **92** as a clear light yellow oil after extraction and concentration. The spectral data for **92** were: IR (thin film) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 4.11 (q, 2 H, J = 7.2 Hz), 4.04 (d, 1 H, J = 12.9 Hz), 3.61 (d, 1 H, J = 12.9 Hz), 3.45 (m, 1 H), 2.91 (m, 1 H), 2.32 (m, 2 H), 1.97 (m, 1 H), 1.87-1.46 (complex, 6 H), 1.25 (t, 3 H, J = 7.2 Hz), 1.27-0.98 (complex, 4 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 140.1, 128.8, 128.1, 126.7, 62.5 (CH), 61.0 (CH_2), 60.2 (CH_2), 59.4 (CH_2), 47.5 (CH), 42.1 (CH), 39.0 (CH_2), 29.5 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 14.2 (CH_3); MS (EI/DP): *m/e* (%) 301 (4), 215 (17), 214 (100), 91 (67), 65 (5); HRMS, *m/e* for $C_{19}H_{27}NO_2$: calcd, 301.2036; found, 301.2033. The fourth and largest band yielded 245 mg (0.815 mmol, 63%) of **91** as a clear colorless oil after extraction and concentration. The spectral data for **91** were: IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.13 (q, 2 H, J = 7.2 Hz), 3.96 (d, 1 H, J = 13.8 Hz), 3.51 (d, 1 H, J = 13.8 Hz), 2.84 (m, 1 H), 2.60 (m, 2 H), 2.50 (m, 2 H), 1.84-1.72 (complex, 4 H), 1.46 (m, 1 H), 1.29 (m, 1 H), 1.24 (t, 3 H, J = 7.2 Hz), 1.22 (m, 1 H), 1.08 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 140.7, 128.5, 128.2, 126.6, 66.5 (CH), 60.2 (CH_2), 59.8 (CH_2), 57.3 (CH_2), 51.0 (CH), 43.0 (CH), 39.1 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 14.2 (CH_3); MS (EI/DP): *m/e*, (%) 301 (11), 215 (17), 214 (100), 213 (9), 91 (38), 65 (3); HRMS, *m/e* for $C_{19}H_{27}NO_2$: calcd, 301.2036; found, 301.2034. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.70; H, 9.03. Found: C, 75.50; H, 9.05.

General Procedure for the Preparation of Isothiuronium Adducts 103 and 109. The general procedure of Speziale[58] was followed. A 10-mL ethanol solution of 10 mmol of the bromide (**33** or **37**) and 760 mg (10 mmol) of thiourea was refluxed with stirring for 12 h. The solution was cooled to 25°C and then to 0-5°C without stirring for 3 h. The resulting adduct separated as a fine white solid which was collected by filtration, washed with several portions of ether and dried. The adduct was used without further purification in the subsequent hydrolysis step. The physical and spectral properties of the products were the following:

Methyl ((*E*)-2-((Isothiuronium)methyl)cinnamate Bromide (103): 2.95 g (8.90 mmol, 89%); mp 215-216°C; IR ($CHCl_3$) 3750-2920, 1715, 1640, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.33 (bs, 2 H), 9.15 (bs, 2 H), 7.96 (d, 1 H, J = 15.6 Hz), 7.86 (m, 1 H), 7.57 (m, 1 H), 7.44 (m, 2 H), 6.65 (d, 1 H, J = 15.6 Hz), 4.77 (s, 2 H), 3.76 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.6, 166.4, 140.4, 133.4, 133.3, 130.9, 130.6, 129.1, 127.5, 120.4, 51.7, 32.3; MS (FAB^+, thioglycerol): 251 (M-Br).

Ethyl ((*E*)-2-(2-(Isothiuronium)ethyl)cinnamate Bromide (109): 3.30 g (9.20 mmol, 92%); mp 173-174°C; IR ($CHCl_3$) 3720-2910, 1715, 1645, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.11 (bs, 4 H), 7.86 (d, 1 H, J =15.6 Hz), 7.73 (m, 1 H), 7.33 (m, 3 H), 6.51 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.43 (t, 2 H, J = 6.9 Hz), 3.07 (t, 2 H, J = 6.9 Hz), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.6, 166.1, 140.9, 138.1, 132.8, 130.4, 130.3, 127.5, 127.0, 120.2, 60.2, 31.3, 30.9, 14.3; MS (FAB^+, thioglycerol): 279 (M-Br).

General Procedure for the Preparation of Isothiuronium Adducts 104, 105, and 106. A 5-mL ethanol solution of 5 mmol of the bromide (**23**, **24** or **82**) and 380 mg (5 mmol) of thiourea was refluxed with stirring for 24 h. The resulting mixture was cooled to 25°C and concentrated *in vacuo* to afford the adduct as a clear colorless glass that was used directly. The physical and spectral properties of the products were the following:

Ethyl (*E*)-6-Isothiuronium-2-hexenoate Bromide (104): 1.47 g (4.95 mmol, 99%); IR (thin film) 3520-2800, 1720, 1660, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.17 (bs, 2 H), 9.05 (bs, 2 H), 6.92 (dt, 1 H, J = 15.6, 6.9 Hz), 5.93 (d, 1 H, J = 15.6 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 3.22 (m, 2 H), 2.33 (m, 2 H), 1.78 (m, 2 H), 1.23 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.8, 166.0, 148.1, 121.4, 60.0, 30.2, 29.6, 26.9, 14.4; MS (FAB^+, thioglycerol): 217 (M-Br).

Ethyl (*E*)-7-Isothiuronium-2-heptenoate Bromide (105): 1.54 g (4.95 mmol, 99%); IR (thin film) 3450-2740, 1750, 1640, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.12 (bs, 2 H), 9.01 (bs, 2 H), 6.88 (dt, 1 H, J = 15.9, 7.2 Hz), 5.88 (d, 1 H, J = 15.9 Hz), 4.11 (q, 2 H, J = 6.9 Hz), 3.20 (m, 2 H), 2.25 (m, 2 H), 1.57 (m, 4 H), 1.21 (t, 3 H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6) δ 169.9, 165.6, 148.9, 121.3, 59.7, 30.6, 29.8, 27.9, 26.1, 14.2; MS (FAB^+, thioglycerol): 231 (M-Br).

1-((*E*)-2-Ethoxycarbonylethenyl)-1-(2-(isothiuronium)ethyl)cyclohexane Bromide (106): 1.75 g (4.80 mmol, 96%); IR (thin film) 3610-2820, 1740, 1665, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.08 (bs, 4 H), 6.74 (d, 1 H, J = 16.2 Hz), 5.81 (d, 1 H, J = 16.2 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 2.96 (m, 2 H), 1.66 (m, 3 H), 1.39 (m, 9 H), 1.22 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.7, 165.7, 154.6, 120.7, 59.9, 55.9, 34.2, 25.7, 25.4, 21.6, 18.5, 14.1; MS (FAB^+, thioglycerol): 285 (M-Br).

General Procedure for the Preparation of Isothiuronium Adducts 107 and 108. A 5-mL ethanol solution of 3.64 mmol of the bromide (**46** or **55**) and 277 mg (3.64 mmol) of thiourea was refluxed with stirring for 120 h. The resulting mixture was cooled to 25°C and concentrated *in vacuo* to yield the adduct as a white tacky solid that was used without further purification. The physical and spectral properties of the products were the following:

(1*S,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-((isothiuronium)-methyl)cyclohexane Bromide (107)**: 1.26 g (3.59 mmol, 99%); IR ($CHCl_3$)

3540-2850, 1720, 1660, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.07 (bs, 4 H), 7.02 (dd, 1 H, J = 15.6, 7.2 Hz), 5.93 (d, 1 H, J = 15.6 Hz), 4.13 (q, 2 H, J = 7.2 Hz), 3.00 (m, 2 H), 2.71 (m, 1 H), 1.84 (m, 1 H), 1.62 (m, 4 H), 1.37 (m, 4 H), 1.22 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.8, 165.5, 148.4, 122.5, 60.0, 40.1, 33.1, 29.1, 27.0 (2), 23.7, 21.7, 14.2; MS (FAB^+, thioglycerol): 271 (M-Br).

(1*R,2*S**)-(±)-1-((*E*)-2-Ethoxycarbonylethenyl)-2-((isothiuronium)-methyl)cyclohexane Bromide (108)**: 1.24 g (3.53 mmol, 97%); IR ($CHCl_3$) 3650-2720, 1730, 1655, 1645 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.03 (bs, 4 H), 6.75 (dd, 1 H, J = 15.6, 6.9 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 3.19 (m, 1 H), 2.94 (m, 1 H), 2.07 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 4 H), 1.22 (t, 3 H, J = 7.2 Hz), 1.17 (m, 3 H), 1.10 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 170.0, 165.6, 151.5, 121.6, 59.8, 45.0, 39.7, 35.5, 31.7, 29.8, 24.9, 24.7, 14.2; MS (FAB^+, thioglycerol): 271 (M-Br).

General Annulation Procedure for the Preparation of Sulfur Products 110, 111, 112, 113, 114, 115, and 116. The general procedure of Speziale[58] was followed. A mixture of 3.64 mmol of the adduct and 2.63 g (46.9 mmol) of KOH in 10 mL of water was refluxed with stirring for 8 h. The mixture was cooled to 25°C and acidified cautiously at 0-5°C by the dropwise addition of a solution of 2 mL of concentrated sulfuric acid in 4 mL of water to a pH of *ca.* 2. The resulting aqueous mixture was extracted twice with ether. The combined ether extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude acid product as either an oil or a solid which was purified by vacuum distillation or by recrystallization from hexane/ether. The physical and spectral properties of the products were the following:

(±)-1,3-Dihydrobenzo[c]thiophene-1-acetic Acid (110): 487 mg (2.51 mmol, 69%); mp 103-104°C; IR ($CHCl_3$) 3300-2720, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.50-9.00 (bs, 1 H), 7.22 (m, 4 H), 5.01 (dd, 1 H, J = 9.6, 4.4 Hz), 4.33

(d, 1 H, J = 14.0 Hz), 4.18 (d, 1 H, J = 14.0 Hz), 3.12 (dd, 1 H, J = 16.8, 4.4 Hz), 2.86 (dd, 1 H, J = 16.8, 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 177.5, 142.3, 140.3, 127.4, 127.0, 125.0, 124.0, 48.9 (CH), 44.1 (CH_2), 36.7 (CH_2); HRMS, *m/e* for $C_{10}H_{10}SO_2$: calcd, 194.0396; found, 194.0401. An analytical sample of **110** was obtained as colorless needles from hexane/ether, mp 107-108°C. Anal. Calcd for $C_{10}H_{10}SO_2$: C, 61.84; H, 5.19. Found: C, 61.76; H, 5.28.

(±)-3,4-Dihydro-1*H*-2-benzothiopyran-1-acetic Acid (116): 553 mg (2.66 mmol, 73%); mp 108-109°C; IR ($CHCl_3$) 3690-2885, 1725cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.80-9.90 (bs, 1 H), 7.20 (m, 4 H), 4.37 (m, 1 H), 3.05 (m, 2 H), 2.98 (m, 3 H), 2.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 136.7, 136.4, 129.9, 127.3, 127.2, 126.6, 43.4 (CH_2), 37.0 (CH), 30.6 (CH_2), 24.1 (CH_2); MS (EI/DP): *m/e* (%) 210 (M+2, 2), 208 (22), 191 (6), 162 (17), 149 (100), 129 (9), 115 (28), 91 (6); HRMS, *m/e* for $C_{11}H_{12}SO_2$: calcd, 208.0553; found, 208.0549. An analytical sample of **116** was obtained as colorless plates from hexane/ether, mp 110-111°C. Anal. Calcd for $C_{11}H_{12}SO_2$: C, 62.44; H, 5.81. Found: C, 62.33; H, 5.80.

(±)-2-Tetrahydrothiopheneacetic Acid (111): 314 mg (2.15 mmol, 59%); bp 72-76°C (0.5 mm Hg); IR (thin film) 3560-2480, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.40-9.80 (bs, 1 H), 3.72 (m, 1 H), 2.89 (m, 2 H), 2.67 (m, 2 H), 2.16 (m, 1 H), 2.01 (m, 2 H), 1.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 178.0, 43.3, 42.0, 36.7, 32.5, 30.0; MS (EI/DP): *m/e* (%) 148 (M+2, 2), 146 (34), 102 (1), 100 (21), 89 (5), 87 (100), 86 (11), 85 (12), 60 (12), 59 (13); HRMS, *m/e* for $C_6H_{10}SO_2$: calcd, 146.0396; found, 146.0396.

(±)-2*H*-Tetrahydrothiopyran-2-acetic Acid (112): 402 mg (2.51 mmol, 69%); mp 73-74°C; IR ($CHCl_3$) 3400-2780, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (bs, 1 H), 3.15 (m, 1 H), 2.69 (m, 2 H), 2.53 (m, 2 H), 2.07 (m, 1 H), 1.90 (m, 2 H), 1.62 (m, 1 H), 1.46 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 40.5, 37.6, 33.8, 28.9, 26.7, 25.4; MS (EI/DP): *m/e* (%) 162 (M+2, 2), 160 (34), 115 (12), 114 (18), 101 (100), 100 (16),

81 (13), 73 (11), 67 (32), 59 (18), 55 (17); HRMS, *m/e* for $C_7H_{12}SO_2$: calcd, 160.0553; found, 160.0549.

(±)-1-(Carboxymethyl)-2-thiaspiro[4.5]decane (113): 552 mg (2.58 mmol, 71%); mp 99-100°C; IR ($CHCl_3$) 3520-2960, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40-11.60 (bs, 1 H), 3.36 (dd, 1 H, J = 11.4, 3.6 Hz), 2.81 (m, 2 H), 2.76 (dd, 1 H, J = 15.9, 3.6 Hz), 2.40 (dd, 1 H, J = 15.9, 11.4 Hz), 1.93 (m, 1 H), 1.77 (m, 1 H), 1.57-1.25 (complex, 10 H); ^{13}C NMR ($CDCl_3$) δ 178.5, 64.0, 50.8, 47.8, 38.0, 34.9, 30.6, 28.2, 26.4, 23.3, 23.1; MS (EI/DP): *m/e* (%) 216 (M+2, 4), 214 (53), 157 (4), 155 (48), 142 (19), 119 (13), 108 (100), 93 (21), 79 (28), 67 (30); HRMS, *m/e* for $C_{11}H_{18}SO_2$: calcd, 214.1022; found, 214.1016. An analytical sample of **113** was obtained as colorless needles from hexane/ether, mp 102-103°C. Anal. Calcd for $C_{11}H_{18}SO_2$: C, 61.65; H, 8.47. Found: C, 61.84; H, 8.35.

(1*R,3a*S**,7a*S**)-(±)-1-(Carboxymethyl)-1, 3, 3a, 4, 5, 6, 7, 7a-octahydrobenzo[c]thiophene (114)**: 538 mg (2.69 mmol, 74%); mp 78-80°C; IR ($CHCl_3$) 3580-2870, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.20-10.40 (bs, 1 H), 3.48 (m, 1 H), 2.90 (m, 1 H), 2.75 (m, 2 H), 2.56 (m, 1 H), 2.40 (m, 1 H), 1.92 (m, 1 H), 1.57 (m, 6 H), 1.37 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.5, 48.2 (CH), 46.3 (CH), 42.2 (CH_2), 42.1 (CH), 34.8 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 23.2 (CH_2), 23.0 (CH_2); MS (EI/DP): *m/e* (%) 202 (M+2, 2), 200 (40), 166 (12), 154 (10), 141 (100), 135 (5), 107 (48), 93 (25), 81 (30), 79 (29), 67 (30), 55 (19); HRMS, *m/e* for $C_{10}H_{16}SO_2$: calcd, 200.0866; found, 200.0869. An analytical sample of **114** was obtained as colorless needles from hexane/ether, mp 81-82°C. Anal. Calcd for $C_{10}H_{16}SO_2$: C, 59.97; H, 8.06. Found: C, 60.26; H, 8.15.

(1*R,3a*S**,7a*R**)-(±)-1-(Carboxymethyl)-1, 3, 3a, 4, 5, 6, 7, 7a-octahydrobenzo[c]thiophene (115)**: 554 mg (2.77 mmol, 76%); mp 129-130°C; IR ($CHCl_3$) 3590-2870, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.40-9.60 (bs, 1 H), 3.29 (m,

1 H), 2.89 (m, 2 H), 2.52 (m, 2 H), 1.94 (m, 2 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.17 (m, 2 H), 1.06 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.1, 53.0 (CH), 48.7 (CH), 48.3 (CH), 40.0 (CH_2), 36.7 (CH_2), 31.8 (CH_2), 30.1 (CH_2), 25.6 (CH_2), 25.5 (CH_2); MS (EI/DP): *m/e* (%) 202 (M+2, 4), 200 (60), 166 (18), 154 (21), 141 (100), 135 (12), 121 (6), 107 (50), 93 (38), 79 (29), 67 (28); HRMS, *m/e* for $C_{10}H_{16}SO_2$: calcd, 200.0866; found, 200.0865. An analytical sample of **115** was obtained as colorless plates from hexane/ether, mp 131-132°C. Anal. Calcd for $C_{10}H_{16}SO_2$: C, 59.97; H, 8.06. Found: C, 59.76; H, 8.01.

Single Crystal X-ray Structure Determination of (1*R,3a*S**,7a*S**)-(±)-1-(Carboxymethyl)-1, 3, 3a, 4, 5, 6, 7, 7a-octahydrobenzo[c]thiophene (114).** A crystal of $C_{10}H_{16}O_2S$, grown from aqueous ethanol, was mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (see Table X) were determined by least squares refinement of the best angular positions for fifteen independent reflections (2θ>15°) during normal alignment procedures using molybdenum radiation (λ=0.71069 Å). Data (1331 independent points after removal of redundant data) were collected at room temperature using a variable scan rate, a θ-2θ scan mode and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 45°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections. As the intensities of these reflections showed less than 5% variation, corrections for decomposition were were deemed unnecessary. Data were corrected for Lorentz, polarization and background effects. Observed reflections [943 ((I>3.0σ(I))] were used for solution of non-hydrogen atom positions by direct methods using MULTAN.[63] Refinement[64] of scale factor, positional and anisotropic thermal parameters for all non-hydrogen atoms were carried out to convergence. The positions of hydrogen atoms were located from a difference Fourier synthesis. Hydrogen atom positions were included in the final cycles of refinement with fixed, isotropic thermal parameters. The final cycle of refinement [function minimized,

TABLE X

CRYSTAL DATA FOR **114**

Formula	$C_{10}H_{16}O_2S$
MWT	200.3
a	14.667(5) Å
b	5.285(1)
c	13.946(5)
α	90°
β	110.00(2)
γ	90
V	1010.0(5) $Å^3$
F(000)	432
μMoK_α	2.732 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.317 g cm^{-3}
Z	4
Space Group	$P2_1/a$
Obs. refl.	943
Refl. meas.	1331
Octants meas.	$\pm$h, k, 1
R/Rw	4.7/6.2%

$\Sigma w(|Fo|-|Fc|)^2]$ led to a final agreement factor, R=4.7%. [R=($\Sigma w| |Fo|-|Fc| | / \Sigma w|Fo|$) x 100]. Scattering factors were taken from Cromer and Mann.[65] In the final stages of refinement a weight factor of 1/σ(F)2 was used. R_w=6.2%. As is normal for solid state organic carboxylic acid groups, molecules exist in hydrogen bonded pairs, O1 H2' and H2 O1', 1.643(4) Å, '=1-x, -y, 1-z. Tables XIII-XVI in Appendix A list bond angles and distances, dihedral angles, positional parameters, and final anisotropic thermal parameters for **114**.

^{1}H-n.O.e. Determinations on Products 89, 90, 91, 92, and 115. Degassed and evacuated 0.024 *M* samples of products **89-92** (5 mg of the product in 0.7 mL of $CDCl_3$) were prepared using the freeze-thaw cycle as described by Neuhaus and Williamson.[55] In the case of **115**, 0.036 *M* samples (5 mg of **115** in $CDCl_3$) were used. In all 5 of these cases, 3 identical samples of each product were prepared. Each sample was then submitted to 3 separate ^{1}H-n.O.e. determinations (for a total of *nine* determinations for each compound) on a Varian XLA-400 superconducting FT instrument using the standard parameters for ^{1}H-n O.e. difference experiments as described by Kinns and Sanders.[56] In the data aquisition, a T-1 delay interval of 7 seconds was used in all cases studied. The standard FIDS data for the irradiated *vs.* nonirradiated spectra were collected in 16 transient blocks with interleave for a total of 48 total transients for each of the comparative spectra. The data as collected was then submitted to standard Fourier analysis and weighing and the % enhancements were determined by direct integral comparison of the irradiated *vs.* nonirradiated spectra for the assigned protons of interest in each compound. In all of the samples studied, the ^{1}H-n.O.e. results observed were reproducible to within ±0.1% enhancement.

Reaction Chronology Study for the Formation of Nitrogen Heterocycles. A 5-mL ethanol solution of 0.57 g (0.62 mL, 5.0 mmol) of ethyl crotonate, 0.54 g (0.55 mL, 5.0 mmol) of benzylamine, 1.06 g (0.74 mL, 5.0 mmol) of

1-iodohexane and 0.56 g (0.77 mL, 5.5 mmol) of triethylamine was heated at reflux according to the standard heterocyclization procedure. The reaction was monitored by GC analysis of 0.15 μL aliquots removed from the reaction at 30-min intervals during the first 3 h and at 1-h intervals thereafter. After 12 h, all of the benzylamine and 1-iodohexane had been consumed. A significant amount (*ca.* 75%) of the ethyl crotonate remained after this time.

Reaction Chronology Study for the Formation of Sulfur Heterocycles. A mixture of 1.24 g (5.0 mmol) of benzylisothiuronium bromide and 0.88 g (5.0 mmol) of ethyl cinnamate was stirred at 23°C with 20% KOH in 4:1 water/ethanol. The reaction was monitored by TLC at 15-min intervals for disappearance of the reactants. After 40 min, the ethyl cinnamate had been completely consumed. Benzyl mercaptan and its cinnamate addition product were formed to only a minor extent during this period.

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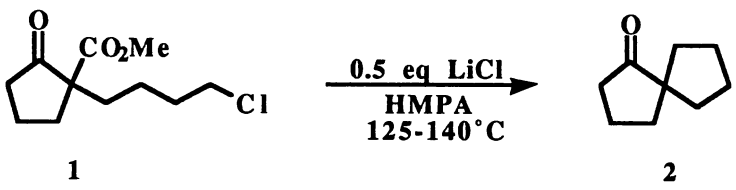
CHAPTER III

A TANDEM NUCLEOPHILIC DECARBOXYXLATION-MICHAEL ADDITION ROUTE TO FUNCTIONALIZED SPIRANES

Introduction

Spiro carbocyclic ring systems are an important structural subunit of many natural products[66-69] and have received much attention in contemporary organic synthesis. Earlier work by Eilerman and Willis[70] illustrated an efficient method for the preparation of spirocyclic products **2** from the reaction of 2-methoxycarbonyl-2-(4-chlorobutyl)cyclo-alkanones **1** with catalytic lithium chloride in HMPA at 125-140°C. This approach is shown in Figure 24. The reaction sequence was initiated by the reaction of β-ketoester **1** with chloride ion (see Figure 25) proceeding through an initial S_N2-type dealkylation-decarboxylation process to afford carbanion intermediate **3** which cyclized in a subsequent intramolecular alkylation reaction to afford **2**. This method used a catalytic amount of lithium chloride (0.5 eq) due to the fact that the chloride ion initially consumed in the decarboxylation step is regenerated in the subsequent intramolecular cyclization.



1 2

Figure 24. Eilerman-Willis Approach to Spirane Preparation.

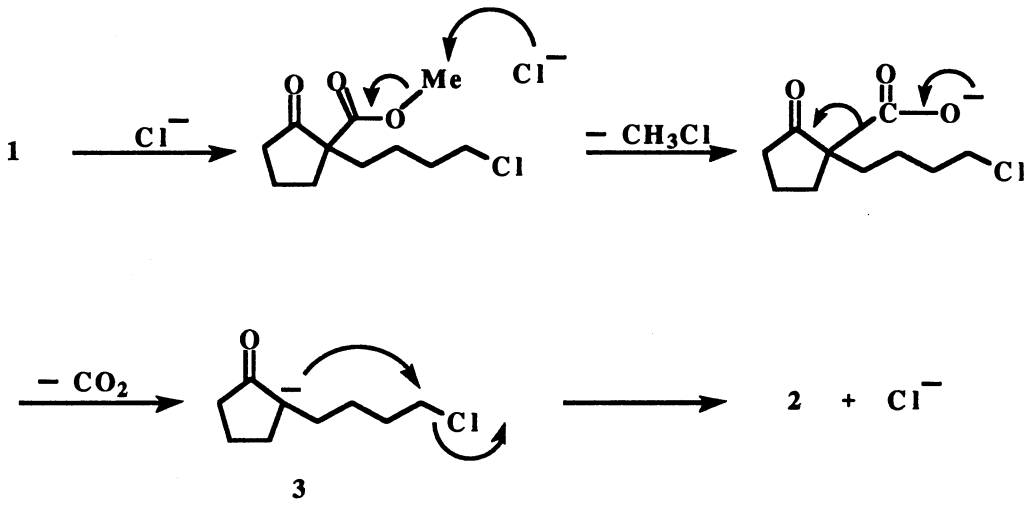


Figure 25. Mechanism for the Preparation of Spirane Product **2**.

In view of the above observations, it was envisioned that a similar approach involving a tandem nucleophilic decarboxylation-Michael reaction sequence resulting from the reaction of a 2-methoxycarbonyl-2-substituted cycloalkanone **4** bearing a side chain incorporating a Michael acceptor with lithium chloride in HMPA could possibly be used to form spirocyclic ring systems **5** bearing differentiated.functionality (see Figure 26). In

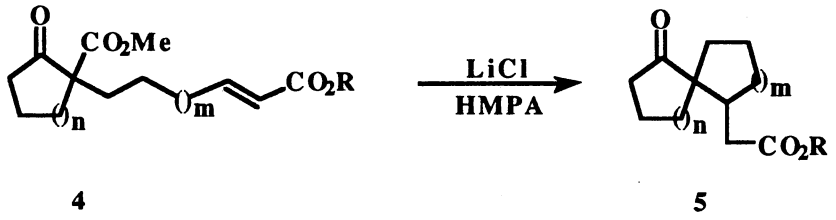


Figure 26. An Approach to Functionalized Spiranes Using a Tandem Decarboxylation-Michael Addition Route.

this study, several goals were set, most notably the devisement of a set of viable reaction conditions that would allow for the process to proceed with the possibility of stereo-chemical selectivity in the products formed.

Results

Synthesis of the Starting Materials. The synthesis of the starting substrates **11a-f** for the decarboxylation-Michael addition sequence is illustrated in Figure 27. Side chain precursors (**9a** and **9b**) incorporating the desired acrylate ester Michael acceptor

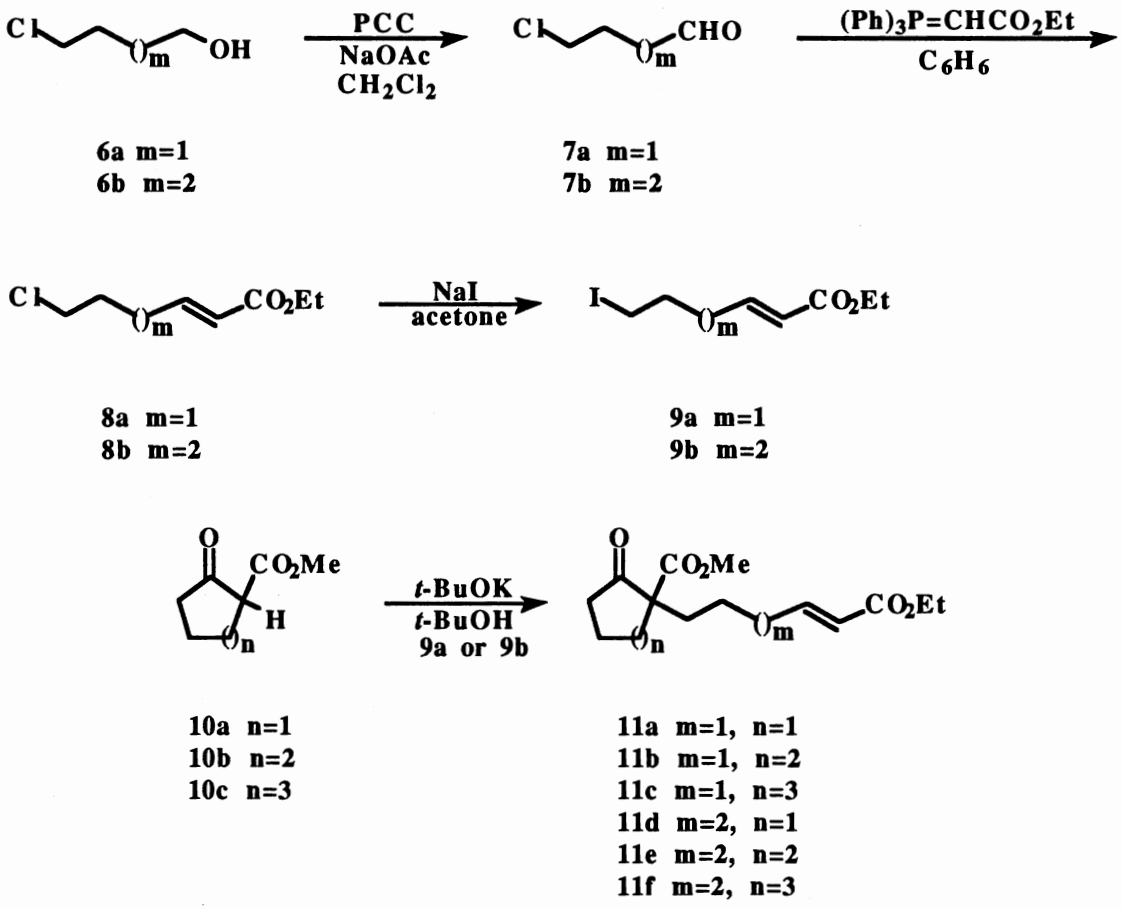


Figure 27. Synthesis of Starting Substrates **11a-f**.

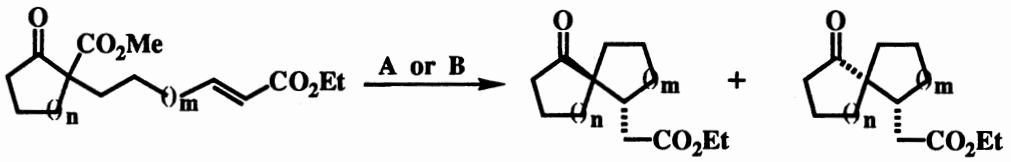
functionality were easily synthesized using a modification of the approach described by Cooke and Widener.[71] The buffered oxidation of 4-chlorobutanol (**6a**) with pyridinium chlorochromate[37] to 4-chlorobutanal (**7a**) followed by Wittig olefination using ethyl (triphenylphosphoranylidene)acetate yielded ethyl (*E*)-6-chloro-2-hexenoate (**8a**) in 57% overall yield. Treatment of **8a** with sodium iodide in refluxing acetone smoothly afforded ethyl (*E*)-6-iodo-2-hexenoate (**9a**). The alkylation of 2-methoxycarbonylcycloalkanones **10a-c** with **9a** using potassium *tert*-butoxide in *tert*-butyl alcohol solvent then afforded the desired starting substrates **11a-c** in an average yield of 63%. The above sequence was also applied to the synthesis of ethyl (*E*)-7-iodo-2-heptenoate (**9b**) from 5-chloro-pentanol (**6b**). The alkylation of **10 a-c** with **9b** using *tert*-butoxide in *tert*-butyl alcohol yielded the 6-ring precursors **11d-f**.

Spirane Formation and Structure Elucidation of the Products. The results of this study on the tandem decarboxylation-Michael addition sequence for the series of 5-ring and 6-ring starting substrates described in the previous section are shown in Table XI. The reaction was run in HMPA using 3 equivalents of anhydrous lithium chloride with the differences in reaction temperature and reaction time being dependent on whether the reaction sequence involved 5-ring or 6-ring closure. Formation of spiro[4.n]alkan-1-one products **12 a-c** and **13 a-c** (5-ring closure) proceeded smoothly at a reaction temperature of 95-100°C with a reaction time of 4 h and gave yields in the range of 55-65%. The stereochemical selectivities ranged from 3:1 in the formation of the spiro[4.5]decan-1-one products (**12b** and **13b**) to 30:1 for the spiro[4.6]undecan-1-ones (**12c** and **13c**). In cases involving a 6-ring closure, it was found that higher reaction temperatures (125-130°C) and a longer reaction time (6 h) were required for the reaction to proceed to completion. When these conditions were employed, yields in the range of 44-54% and stereochemical selectivities ranging from 21:1 to 26:1 were observed. The lower yields from this series of substrates likely derives from the increased entropy required to bring

the reactive centers together to close the 6-membered ring.[72]

TABLE XI

THE PREPARATION OF FUNCTIONALIZED SPIRANES SPIRANES USING A TANDEM DECARBOXYLATION-MICHAEL ADDITION REACTION SEQUENCE.



11 a-f **12 a-f** **13 a-f**

Starting Material	m	n	**12 : 13**	Yield (%) **(12 + 13)**	Reaction Conditions[a]
11a	1	1	20 : 1	62	A
11b	1	2	3 : 1	56	A
11c	1	3	30 : 1	62	A
11d	2	1	24 : 1	50	B
11e	2	2	21 : 1	44	B
11f	2	3	26 : 1	54	B

[a]A: 3 eq. LiCl, HMPA, 95-100°C, 4 h. B: 3 eq. LiCl, HMPA, 125-130°C, 6 h.

The procedure, as devised, differs from that used by Eilerman and Willis in requiring excess lithium chloride; this derives from the fact that chloride ion is not generated in the Michael addition step as it is in the alkylation where chloride was displaced from **3** in the cyclization step. The procedure was performed in HMPA, DMPU (1,3-dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone) and *N*-methylpyrrolidine but it was found that HMPA

was far superior in this current application. The use of HMPA as the solvent allowed for both lower reaction temperatures and shorter reaction times and is easily removed at the end of the reaction using an acidic workup.

The inherent reversibility of the Michael addition process leads to overall thermodynamic control in the cyclization step. The elucidation of the stereochemistry of the major and minor products resulting from the 5-ring spiroannulation sequence (**12a-c** and **13a-c**) was accomplished by a combination of chemical degradation and single-crystal X-ray diffraction studies. The first degradative study attempted is outlined in Figure 28. It was expected that selective sodium borohydride reduction of the ketone functionality[78] followed by base hydrolysis, neutralization and mild acidification to pH 3-4 would result in lactonization (to give **17**) for isomer **13** having the ketone and ethoxycarbonylmethyl functions cis. In the trans isomer **12**, this sequence was expected to yield hydroxy acid **15** since the trans oriented groups would not be expected to readily lactonize.

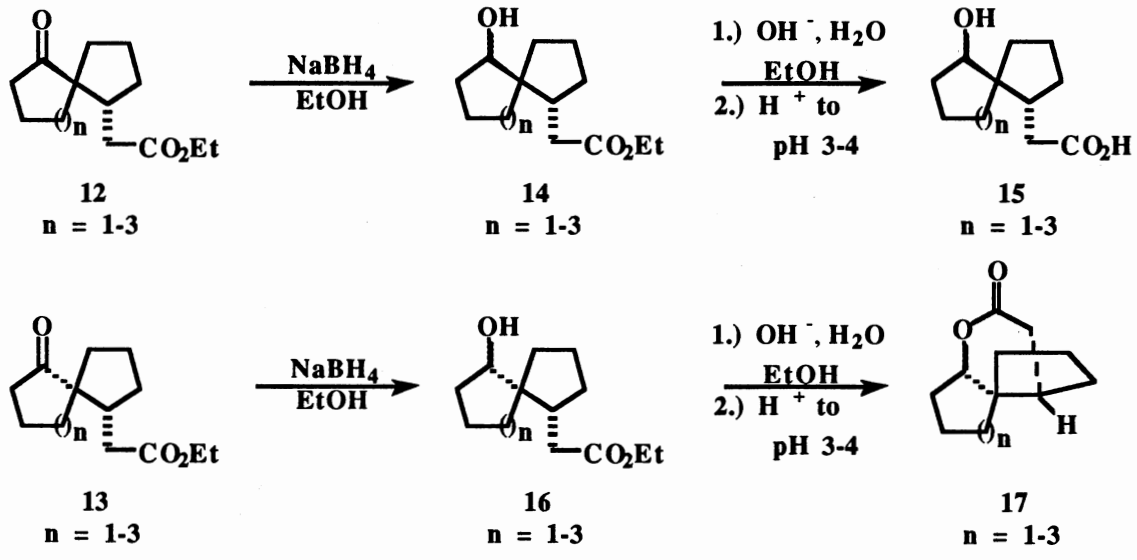


Figure 28. Chemical Degradation Proof Method 1.

The results of this chemical degradative scheme are summarized in Figure 29. Reduction of the trans major products **12a** and **12b** smoothly afforded hydroxy esters **14a** and **14b** which, upon base hydrolysis and acidification, cleanly yielded the hydroxy acid products **15a** and **15b** thus implying that **12a** and **12b** had the trans stereochemistry. However, in the case of the cis minor products **13 a-c**, it was not possible to avoid

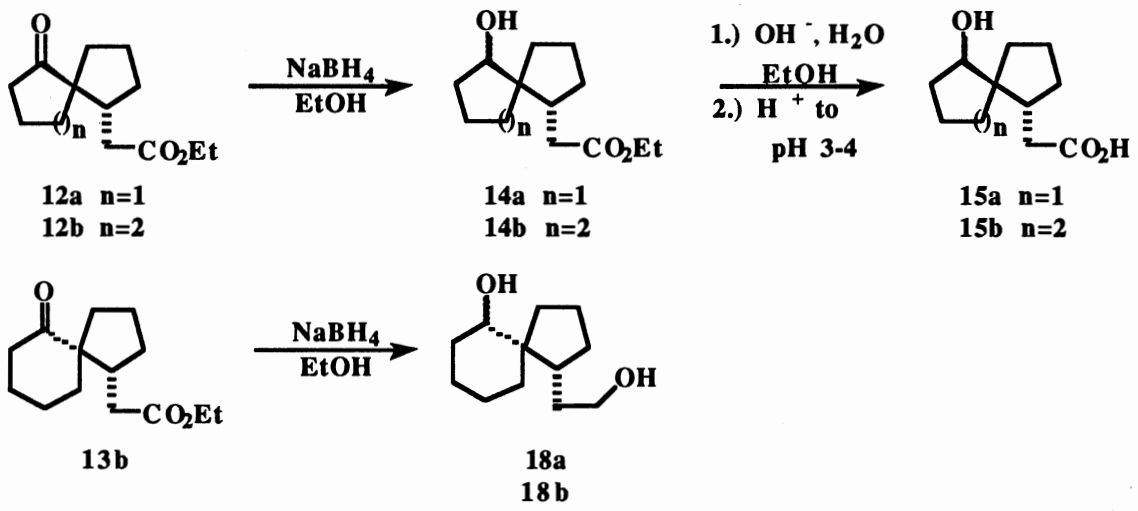


Figure 29. Results of Chemical Degradation Proof Method 1 for **12a**, **12b** and **13b**.

overreduction[73] and the diol products **18a** and **18b** were obtained as a pair of diastereomers from the reduction of **13b** even when 0.25 equivalents of sodium borohydride were used. To account for this observation, it would seem reasonable that the relative orientation of the ketone and ester groups in the cis products is such that initial reduction of the ketone places the oxygen-bound borohydride moiety directly over the ester group as in **20** (see Figure 31) facilitating the unexpected reduction of the ester. Literature

precedent does exist for the activation of the borohydride moiety by heteroatom substitution.[74] In cases derived from the 7-ring keto ester **11c**, overreduction occurred (see Figure 30) in both product isomers to afford the diol. This observation could result from the increased conformational flexibility in this ring system that would permit the oxygen-bound borohydride moiety to approach the ester functionality as in **21** (see Figure 31) such that the second reduction could occur.

12c **19**

Figure 30. Results of Chemical Degradation Proof Method 1 on Product **12c**.

20 **21**

Figure 31. Structures **20** and **21**.

In view of these observations, a second degradation scheme was devised in an attempt to avoid the possibility of overreduction of the ester functionality. In this approach, it was thought that the initial conversion of the ester group to the corresponding carboxylic acid, which would not be easily reduced by borohydride,[75] followed by reduction (see Figure 32) would avoid the problem of overreduction observed in the previous degradation scheme. It was envisioned that base hydrolysis of the ester functionality followed by sodium borohydride reduction of the ketone group[76] and subsequent mild acidification to pH 3-4 would result in lactonization (to give **17**) of the isomer **13** having the ketone and ethoxycarbonylmethyl groups cis. Conversely, as in the previous degradation scheme, the trans isomer **12** was expected to afford a hydroxy acid product (**15**) since the trans oriented groups would not be expected to lactonize.

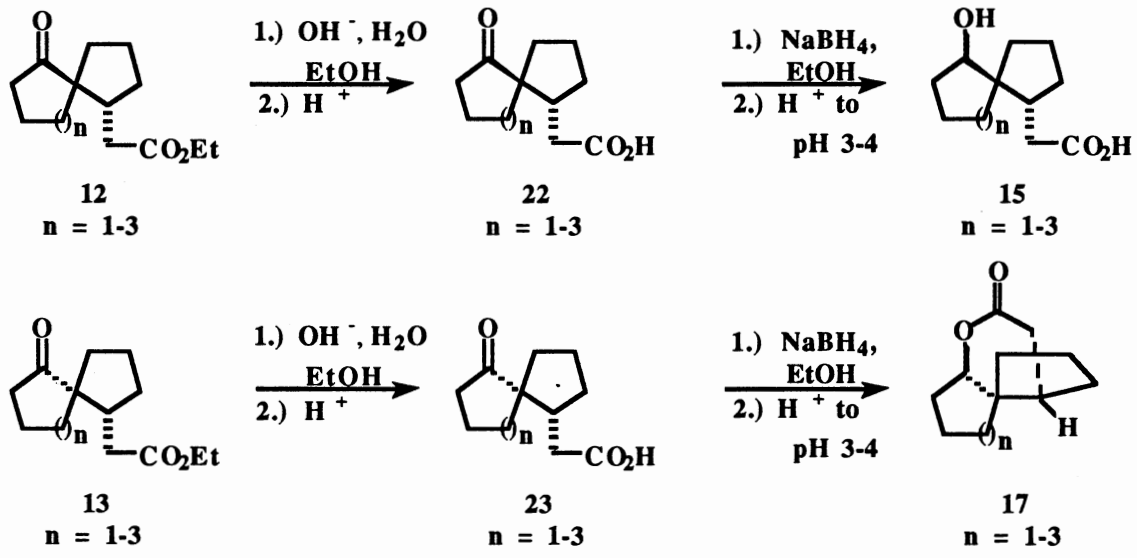


Figure 32. Chemical Degradation Proof Method 2.

The results of this second chemical degradative scheme are shown in Figure 33. Base hydrolysis of the trans major products **12a** and **12b** yielded keto acids **22a** and **22b** which, upon reduction and acidification, smoothly yielded the hydroxy acid products **15a** and **15b**. In the case of the cis minor products **13a** and **13b**, the employment of the same degradative scheme cleanly afforded the cis lactone products **17a** and **17b**. However, in the case of the trans major product **12c**, the trans lactone **24** was isolated as the only degradation product after implementation of the base hydrolysis-reduction sequence.

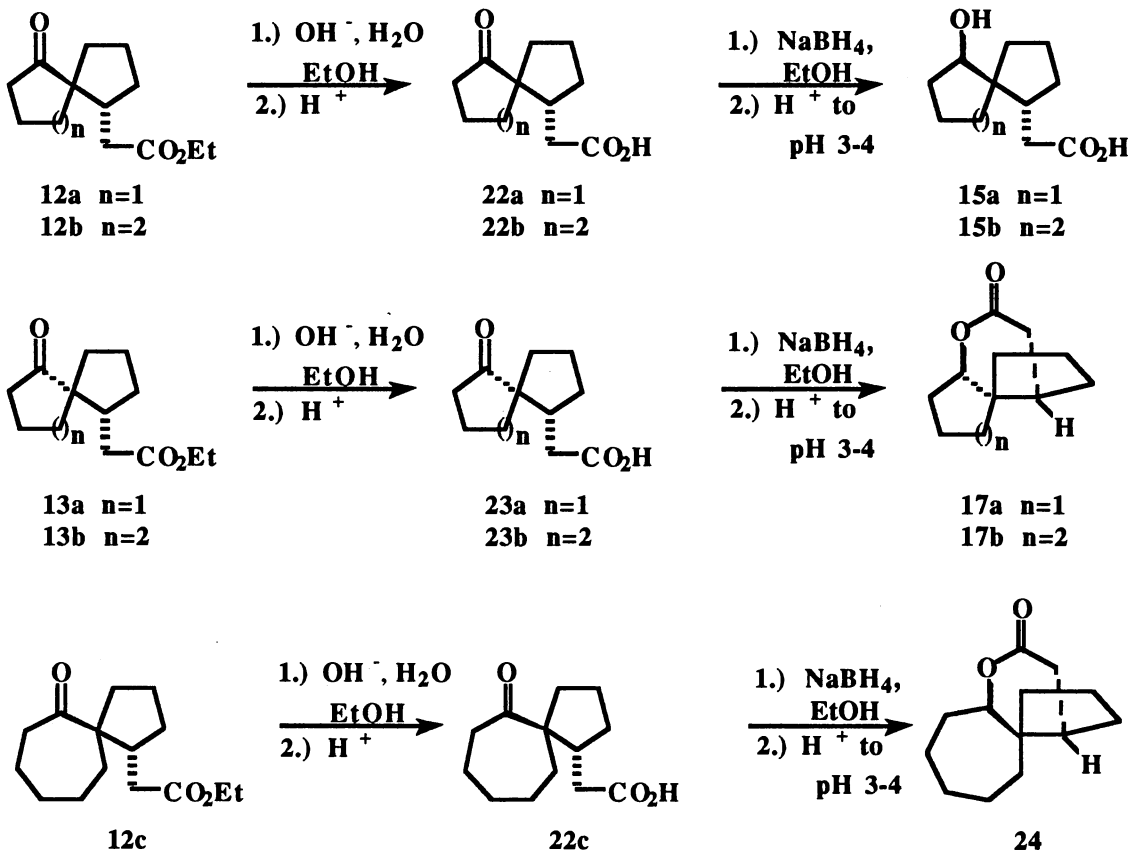
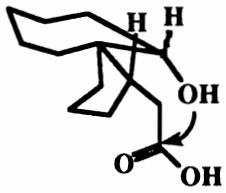


Figure 33. Results of Chemical Degradation Proof Method 2 for **12a-c** and **13a-b**.

Apparently, the increased conformational flexibility in this ring system allows the carboxyl group to approach the hydroxyl functionality as in **25** (see Figure 34) such that the observed lactonization process can occur.



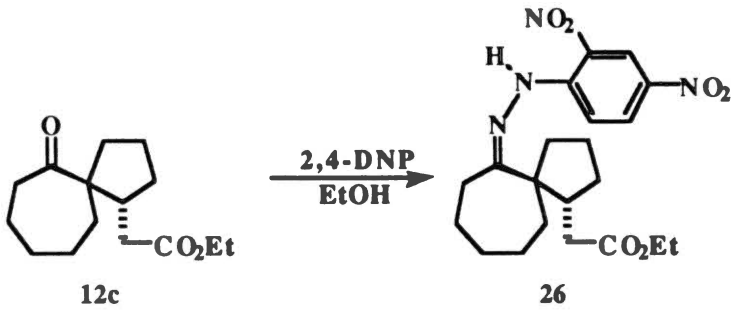
25

Figure 34. Structure **25**.

From the results of the chemical degradation sequences, the stereochemistry of major products **12a** and **12b** was assigned as being trans while the minor products **13a** and **13b** were assigned the cis configuration. The trans stereochemistry of major product **12c** was assigned formally based on a single crystal X-ray diffraction structure obtained on its 2,4-dinitrophenylhydrazone derivative **26**. The preparation[79] of derivative **26** is shown in Figure 35. The CHEM3D diagram for **26** as determined by single crystal X-ray diffraction techniques is illustrated in Figure 36.

In an attempt to determine the stereochemistry of products **12d** and **12f**, the *p*-bromoanilide derivatives, **29a** and **29c**, were prepared from the corresponding keto acids **27d** and **27f**. If these amides were solids, as expected, it was thought that single crystal X-ray diffraction techniques could be utilized to elucidate the stereochemistry of the spirocyclic framework. Despite several attempts using a number of different solvent combinations and recrystallization techniques, it proved impossible to obtain crystals

suitable for a structure determination. The preparation of amides **29a** and **29c** is shown in Figure 37.



12c 26

Figure 35. Preparation of 2,4-DNP Derivative **26**.

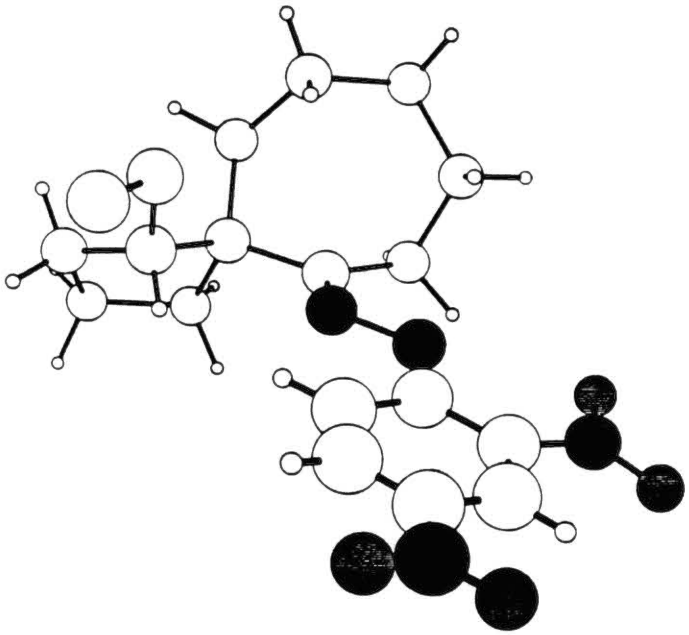


Figure 36. The CHEM3D Diagram for **26**. (The Protons of the Spirocyclic Ring System and the Ethoxycarbonyl Portion of the Acetate Side Chain attached at C-1 have been omitted for viewing clarity.)

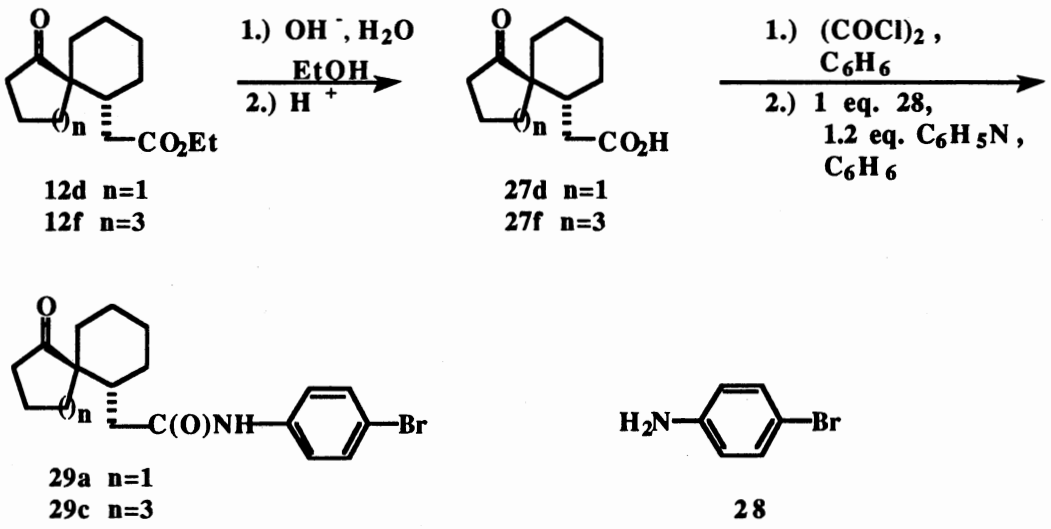


Figure 37. Preparation of Amides **29a** and **29c**.

The stereochemistry of products **12d**, **12e**, and **13d** was tenatively assigned by using the same chemical degradation sequence and reasoning as outlined in Figure 32. Base hydrolysis of the major products **12d** and **12e** yielded ketoacids **27d** and **27e** which, upon reduction[76] and acidification, smoothly afforded hydroxy acid products **30d** and **30e**. In the case of **13d**, the employment of an identical sequence of reactions yielded lactone **32** as the only product. The results of this chemical proof are shown in Figure 38. Reference to molecular models suggests a lack of appreciable ring strain difference in the lactone products derived form the cis and trans spirocyclic compounds in this series. Thus, the stereochemical assignments for these products are considered to be tentative at this time and merit further investigation.

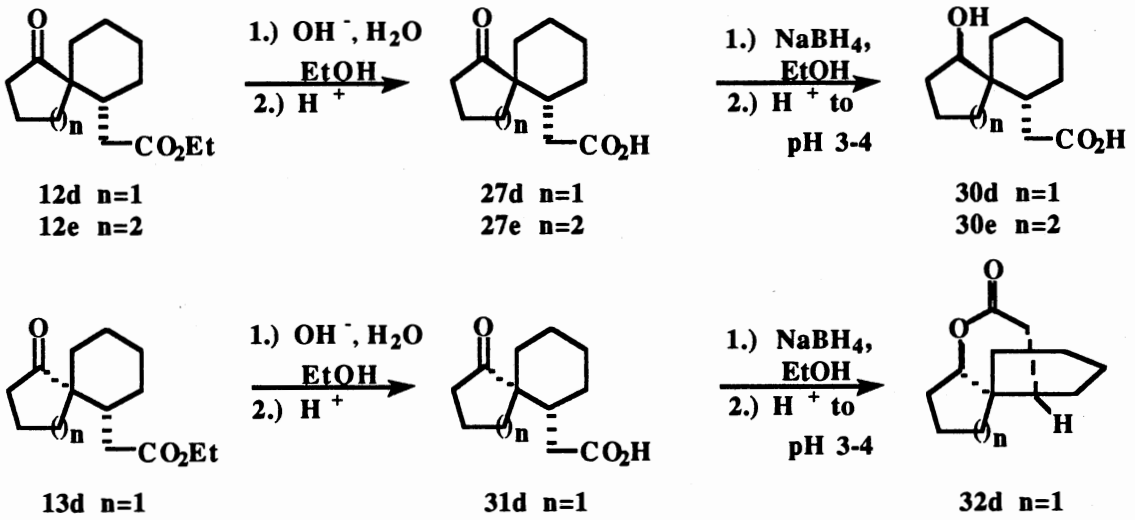


Figure 38. Results of Chemical Degradation Proof Method 2 on **12d**, **12e**, and **13d**.

Experimental

All solvents were purified by distillation or vacuum distillation prior to use. Anhydrous lithium chloride and 2-methoxycarbonylcyclopentanone were used as received from Aldrich Chemical Co. 2-Methoxycarbonylcyclohexanone and 2-methoxycarbonyl-cycloheptanone were prepared and purified by adaptations of literature methods.[77] All reactions were run under an atmosphere of dry nitrogen. Reactions were monitored by one of the following methods: 1) TLC on hard layer silica gel GF plates (Analtech No. 21521) with UV or phosphomolybdic acid detection or 2) capillary GC (Varian 3400) with FI detection on a 0.1 mm x 6 m SE-30 column programmed between 100-300°C. Preparative separations were performed using one of the following methods: 1) PTLC on 20 cm x 20 cm silica gel GF plates (Analtech No. 02015) or 2) flash chromatography[61] on

silica gel (Grace, grade 62, 60-200 mesh) containing UV active phosphor (Sylvania 2282); in each case, band elution was monitored by a hand-held UV lamp. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded with a PE-681 instrument and are referenced to polystyrene. ^{1}H-NMR and ^{13}C-NMR spectra were measured as solutions in deuterated solvents at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively, on a Varian XL-300 or a Varian XLA-400 superconducting FT instrument; chemical shifts are reported in δ units relative to internal Me_4Si. Mass spectra (MS) were obtained using a VG TS-250 instrument; high resolution mass spectra (HRMS) were obtained using a VG ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Ethyl (*E*)-6-Iodo-2-hexenoate (9a) and Ethyl (*E*)-7-Iodo-2-heptenoate (9b). The preparations of **9a** and **9b** from 4-chlorobutanol (**6a**) and 5-chloropentanol (**6b**) are described in an earlier portion of this thesis (see page 18).

General Procedure for the Preparation of (±)-2-Methoxycarbonyl-2-((*E*)-5-ethoxycarbonyl-4-pentenyl)cycloalkanones (11a, 11b, and 11c). A solution of potassium *tert*-butoxide was generated by dissolving 1.06 g (27.1 mg-atm) of potassium metal in 70 mL of *tert*-butyl alcohol at 40-50°C. The solution was cooled to 20°C and 27.1 mmol of the 2-methoxycarbonylcycloalkanone (**10a**, **10b**, or **10c**) was added with stirring. After stirring for 1 h at 20°C, 7.26 g (27.1 mmol) of ethyl (*E*)-6-iodo-2-hexenoate (**9a**) was added dropwise and the reaction was refluxed for 18 h. The reaction was cooled to 20°C and poured into 125 mL of 0.5 *M* HCl. The resulting solution was extracted twice with ether and the combined ether extracts were washed with 0.5 *M* HCl, water, saturated aqueous $NaHCO_3$, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil. The oil was purified by vacuum distillation using a Kugelrohr apparatus. The physical and spectral properties of the products were the following:

(±)-2-Methoxycarbonyl-2-((*E*)-5-ethoxycarbonyl-4-pentenyl)-cyclopentanone (11a): 5.40 g (19.1 mmol, 71.0%); bp 130-136°C (0.5 mm Hg); IR (thin film) 1750, 1730, 1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (dt, 1 H, J = 15.9, 7.0 Hz); 5.84 (d, 1 H, J = 15.9 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.37 (s, 3 H), 2.48 (m, 2 H), 2.26 (m, 2 H), 1.94 (m, 2 H), 1.50 (m, 2 H), 1.31 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 214.4, 171.2, 166.3, 147.9, 121.7, 60.1, 60.0, 52.4, 37.7, 33.2, 32.7, 32.0, 23.2, 19.4, 14.1; MS (CI, isobutane): *m/e* (%) 283 (M+1, 88), 237 (85), 219 (36), 205 (100), 177 (23).

(±)-2-Methoxycarbonyl-2-((*E*)-5-ethoxycarbonyl-4-pentenyl)-cyclohexanone (11b): 4.50 g (15.2 mmol, 59%); bp 140-145°C (0.5 mm Hg); IR (thin film) 1735, 1730, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 7.0 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 6.9 Hz), 3.76 (s, 3 H), 2.46 (m, 2 H), 2.22 (m, 2 H), 2.03 (m, 1 H), 1.97-1.36 (complex, 9 H), 1.30 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 207.5, 172.2, 166.4, 148.2, 121.5, 60.6, 59.9, 52.1, 40.9, 36.0, 34.0, 32.2, 27.4, 22.7, 22.4, 14.1; MS (CI, isobutane): *m/e* (%) 297 (M+1, 100), 251 (19), 233 (27), 213 (14), 191 (23), 111 (20).

(±)-2-Methoxycarbonyl-2-((*E*)-5-ethoxycarbonyl-4-pentenyl)-cycloheptanone (11c): 4.85 g (15.6 mmol, 60%); bp 158-162°C (0.5 mm Hg); IR (thin film) 1745, 1730, 1720, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92 (dt, 1 H, J = 15.6, 6.8 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.73 (s, 3 H), 2.63 (m, 1 H), 2.46 (m, 1 H), 2.18 (m, 4 H), 1.95 (m, 1 H), 1.80-1.32 (complex, 9 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 209.2, 172.7, 166.3, 148.1, 121.5, 62.5, 59.9, 52.0, 41.9, 34.8, 32.7, 32.2, 29.7, 25.4, 24.7, 23.0, 14.1; MS (CI, isobutane): *m/e* (%) 311 (M+1, 100), 205 (12), 171 (50), 159 (18).

General Decarboxylation-Michael Addition Procedure for the Formation of 5-Ring Spiranes (12a-c and 13a-c). A solution of 6.7 mmol of the (±)-2-methoxycarbonyl-2-((*E*)-5-ethoxycarbonyl-4-pentenyl)cycloalkanone (**11a**, **11b**,

or **11c**) and 0.82 g (19.3 mmol) of anhydrous lithium chloride in 15-20 mL of anhydrous hexamethylphosphoramide (HMPA) was stirred at 95-100°C for 4 h. The resulting brown reaction mixture was cooled to 25°C, poured into 50 mL of 0.5 *M* HCl and extracted 3x with ether. The combined ether extracts were washed with 0.5 *M* HCl, water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by PTLC using the following elution sequence: 99:1 hexane/ether (2x), 98:2 hexane/ether (2x), 96:4 hexane/ether (2x) and 95:5 hexane/ether (3x). This elution procedure afforded the major and minor diastereomeric products in relatively high purity. In all cases, the highest R_f band was the minor isomer, the middle band contained a small amount of a mixture and the low R_f band gave the major isomer. The following compounds were isolated:

(5*R,6*R**)-(±)-6-(Ethoxycarbonylmethyl)spiro[4.4]nonan-1-one (12a)**: 850 mg (3.79 mmol, 59%); IR (thin film) 1745, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (q, 2 H, J = 7.2 Hz), 2.60 (m, 1 H), 2.26 (d, 2 H, J = 8.1 Hz), 2.19, (m, 1 H), 2.16-1.82 (complex, 5 H), 1.71 (m, 4 H), 1.59 (m, 1 H), 1.35 (m, 1 H), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 221.9, 172.2, 59.9, 58.1, 41.0, 37.4, 37.2, 35.5, 31.7, 30.6, 22.3, 19.0, 13.8; MS (EI/DP): *m/e* (%) 224 (M^+, 35), 196 (29), 179 (35), 150 (30), 137 (100), 136 (65), 128 (42), 122 (50), 108 (52), 97 (46), 94 (69), 79 (54). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 8.99. Found: C, 68.98; H, 8.69.

(5*R,6*S**)-(±)-6-(Ethoxycarbonylmethyl)spiro[4.4]nonan-1-one (13a)**: 50 mg (0.22 mmol, 3%); IR (thin film) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (q, 2 H, J = 7.2 Hz), 2.46 (m, 1 H), 2.27 (m, 4 H), 2.03 (m, 4 H), 1.81 (m, 3 H), 1.55 (m, 3 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 222.8, 173.3, 60.2, 57.7, 44.2, 39.0, 38.2, 37.0, 35.7, 32.4, 23.3, 19.9, 14.2; MS (EI/DP): *m/e* (%) 224 (M^+, 26), 198 (12), 196 (36), 179 (41), 150 (33), 137 (100), 136 (53), 122 (46), 97 (52), 79 (54).

(5*R,6*R**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.5]decan-6-one (12b)**: 640 mg (2.69 mmol, 42%); IR (thin film) 1730, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (q, 2 H, J = 7.2 Hz), 2.44 (m, 2 H), 2.40 (m, 1 H), 2.10 (m, 1 H), 2.07-1.55 (complex, 12 H), 1.40 (m, 1 H), 1.28 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 213.2, 172.9, 60.0, 57.9, 39.7, 39.2, 35.0, 34.9, 31.3, 29.6, 26.7, 21.5, 21.4, 14.0; MS (EI/DP): *m/e* (%) 238 (M^+, 16), 220 (41), 193 (38), 151 (100), 111 (60), 98 (86), 94 (46), 93 (47), 81 (66), 79 (68), 67 (77), 55 (75). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31. Found: C, 69.90; H, 9.13.

(5*R,6*S**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.5]decan-6-one (13b)**: 210 mg (0.88 mmol, 14%); IR (thin film) 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7.2 Hz), 2.46 (m, 2 H), 2.25 (m, 1 H), 2.13 (m, 3 H), 2.04-1.36 (complex, 11 H), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 213.7, 173.5, 60.1, 59.2, 44.1, 40.3, 38.0. 35.7, 35.1, 30.0 26.5, 22.4, 21.2, 14.1; MS (EI/DP): *m/e* (%) 238 (M^+, 20), 220 (39), 191 (42), 151 (100), 98 (72), 93 (46), 81 (68), 67 (70), 55 (73).

(5*R, 6*R**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.6]undecan-6-one (12c)**: 980 mg (3.89 mmol, 60%); IR (thin film) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7.0 Hz), 2.57 (m, 2 H), 2.52 (m, 1 H), 2.15 (m, 1 H), 2.08-1.40 (complex, 14 H), 1.33 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 216.8, 172.8, 60.2, 60.1, 42.9, 42.3, 36.7, 35.5, 30.9, 30.7, 30.5, 26.2, 25.3, 22.0, 14.1; MS (EI/DP): *m/e* (%) 252 (M^+, 19), 206 (44), 165 (77), 136 (82), 112 (70), 94 (60), 93 (62), 81 (100), 79 (75), 67 (83), 55 (80). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.38; H 9.59. Found: C, 70.57; H, 9.64.

(5*R,6*S**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.6]undecan-6-one (13c)**: 30 mg (0.12 mmol, 2%); IR (thin film) 1735, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (q, 2 H, J = 7.0 Hz), 2.53 (m, 2 H), 2.37 (m, 1 H), 2.23 (m, 1 H), 2.05 (m, 1 H), 1.95-1.51 (complex, 11 H), 1.48-1.33 (complex, 3 H), 1.17 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 217.7, 172.9, 61.3, 60.3, 47.8, 43.5, 37.7, 36.0, 34.9, 31.4, 30.6,

26.7, 25.9, 22.5, 14.2; MS (EI/DP): *m/e* (%) 252 (M^+, 26), 206 (39), 165 (72), 137 (59), 94 (63), 81 (100), 79 (78), 67 (72), 55 (80).

General Procedure for the Sodium Borohydride Reduction of 12a, 12b, and 12c (14a, 14b, and 19). The procedure of Fieser and Ettorre[78] was followed. A 5-mL ethanol solution of 2.00 mmol of the spiro compound was added to a slurry of 91 mg (2.40 mmol) of sodium borohydride in 10 mL of ethanol and the resulting mixture was stirred at room temperature for 8-10 h. The mixture was then cooled to 0 °C and 2 mL of 1.0 *M* HCl was slowly added dropwise over the course of 5 min. The ethanol was removed under vacuum, 15 mL of water was added and the resulting mixture was extracted twice with ether. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The products were isolated pure and used directly in the hydrolysis. The physical and spectral data were:

(5*R,6*R**)-(±)-6-(Ethoxycarbonylmethyl)-spiro[4.4]nonan-1-ol (14a)**: 384 mg (1.70 mmol, 85%); IR (thin film) 3580-3300, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (q, 2 H, J = 7.2 Hz), 3.77 (m, 1 H), 2.86 (bs, 1 H), 2.30 (m, 1 H), 2.10 (m, 2 H), 1.84 (m, 4 H), 1.72-1.60 (complex, 6 H), 1.32 (m, 2 H), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 174.3, 75.6, 60.3, 54.8, 40.0, 35.3, 31.3, 30.0 (2), 28.9, 21.6, 18.8, 14.1; HRMS, *m/e* for $C_{13}H_{22}O_3$: calcd, 226.1569; found, 226.1567.

(5*R,6*R**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.5]decan-6-ol (14b)**: 418 mg (1.74 mmol, 87%); IR (thin film) 3600-3200, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (q, 2 H, J = 6.9 Hz), 3.33 (m, 1 H), 2.72 (bs, 1 H), 2.40 (m, 2 H), 2.15 (m, 1 H), 1.92-1.44 (complex, 13 H), 1.31 (m, 1 H), 1.27 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 174.6, 71.6, 60.4, 49.2, 39.3, 34.0, 32.1, 30.1, 28.9, 27.4, 24.8, 21.5, 21.3, 14.1; HRMS, *m/e* for $C_{14}H_{24}O_3$: calcd, 240.1725; found, 240.1726.

(5*R,6*R**)-(±)-1-(2-Hydroxyethyl)spiro[4.6]undecan-6-ol (19)**: 352 mg (1.66 mmol, 83%); mp 90-91°C; IR ($CHCl_3$) 3650-3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72, (m, 1 H), 3.61 (m, 1 H), 2.70 (bs, 2 H), 2.07 (m, 2 H), 1.95 (m, 2 H), 1.80 (m, 2 H), 1.68-1.32 (complex, 11 H), 1.21 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 80.1, 62.6, 50.3, 45.1, 36.1, 34.0, 33.8, 32.5, 28.0, 27.1, 22.3, 21.8, 21.3; HRMS, *m/e* for $C_{13}H_{24}O_2$: calcd, 212.1776; found, 212.1770.

General Procedure for the Hydrolysis of 14a and 14b (15a and 15b). A 5-mL ethanol solution of 1.00 mmol of the hydroxyester was added to 10 mL of 1.0 *M* NaOH and the resulting solution was heated with stirring at 40 °C for 2 h. The solution was cooled and carefully acidified to a pH of *ca.* 3 by dropwise addition of 6.0 *M* HCl. The resulting solution was stirred at 23 °C for 2 h, then extracted twice with ether. The combined organic extracts were washed with water and saturated NaCl, then dried over Na_2SO_4 and concentrated *in vacuo* to give the following products.

(5*R,6*R**)-(±)-6-(Carboxymethyl)spiro[4.4]nonan-1-ol (15a)**: 176 mg (0.88 mmol, 89%); IR (thin film) 3540-2500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (bs, 2 H), 3.83 (m, 1 H), 2.36 (m, 1 H), 2.15 (m, 2 H), 1.98 (m, 2 H), 1.80 (m, 1 H), 1.74-1.42 (complex, 5 H), 1.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 179.2, 75.8, 54.9, 39.7, 35.1, 31.5, 31.3, 30.1, 29.0, 21.7, 18.8; MS (CI, isobutane): *m/e* (%) 198 (2), 180 (8), 163 (11), 139 (13), 121 (100), 79 (30).

(5*R,6*R**)-(±)-1-(Carboxymethyl)spiro[4.5]decan-6-ol (15b)**: 193 mg (0.91 mmol, 91%); mp 123-124°C; IR ($CHCl_3$) 3520-2540, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (bs, 2 H), 3.40 (m, 1 H), 2.42 (m, 2 H), 2.16 (m, 1 H), 1.85 (m, 2 H), 1.73-1.40 (complex, 5 H), 1.36-1.12 (complex, 6 H), 1.00-0.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 179.3, 71.9, 49.1, 39.2, 33.9, 32.0, 30.1, 29.0, 27.4, 24.8, 21.6, 21.3; MS (CI, isobutane): *m/e* (%) 212 (4), 195 (30), 194 (55), 152 (19), 135 (100), 93 (28), 67 (32).

(5*R,6*S**)-(±)-1-(2-Hydroxyethyl)spiro[4.5]decan-6-ol (18a and 18b).** A 1-mL ethanol solution of 100 mg (0.42 mmol) of **13b** was added to a slurry of 19.1 mg (0.52 mmol) of sodium borohydride in 3 mL of ethanol and the resulting mixture was stirred at room temperature for 8 h. The mixture was then cooled to 0 °C and 0.5 mL of 1.0 *M* HCl was slowly added dropwise over the course of 5 min. The ethanol was removed under vacuum, 10 mL of water was added and the resulting mixture was extracted twice with ether. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. ^1H and ^{13}C-NMR analysis indicated that the crude reduction isolate was a mixture of two diastereomeric diol products. The mixture was passed through a 5.0 cm silica gel plug with 50% ether in hexane to remove any polymeric material and then concentrated *in vacuo*. The resulting clear oil was purified by HPLC on a Waters 590 programmable HPLC, using a reverse phase Dynamax C-18 prep column eluted with 30:70 water:methanol. At a flow rate of 10 mL/min, 250 μL injections containing 50 mg of the product mixture could be separated; a total of two injections were made. The first and major band (R_T = 13.8 min) afforded 40 mg (0.20 mmol, 48%) of diastereomeric diol product **18a** as a white solid after concentration of the collected eluent and extraction with ether, mp 49-50°C. The spectral data for **18a** were: IR ($CHCl_3$) 3650-3060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (m, 1 H), 3.60 (m, 1 H), 3.45 (m, 1 H), 1.80-1.52 (complex, 7 H), 1.48-1.03 (complex, 12 H); ^{13}C NMR ($CDCl_3$) δ 73.9, 63.0, 48.5 (2), 37.9, 33.4, 32.9, 32.7, 29.8, 24.4, 24.1, 23.3; HRMS, *m/e* for $C_{12}H_{22}O_2$: calcd, 198.1620; found, 198.1623. The second band (R_T = 19.8 min) afforded 26 mg (0.13 mmol, 31%) of diastereomeric diol product **18b** as a white solid after concentration of the collected eluent and extraction with ether, mp 56-57°C. The spectral data for **18b** were: IR ($CHCl_3$) 3635-3060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (m, 2 H), 3.52 (m, 1 H), 2.42 (bs, 2 H), 1.88 (m, 1 H), 1.74 (m, 1 H), 1.66 (m, 5 H), 1.64-1.22 (complex, 8 H),

1.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 71.1, 62.0, 49.4, 44.5, 31.8, 30.7, 30.3, 30.0, 28.7, 21.8, 21.2, 19.6; HRMS, *m/e* for $C_{12}H_{22}O_2$: calcd, 198.1620; found, 198.1619.

General Procedure for the Hydrolysis of Ketoesters 12a, 12b, and 12c to Afford Ketoacids 22a, 22b, and 22c. A 5-mL ethanol solution of 1.00 mmol of the ketoester was added to 10 mL of 1.0 *M* NaOH and the resulting solution was heated with stirring at 40 °C for 2 h. The solution was cooled and carefully acidified to a pH of *ca.* 3 by dropwise addition of 6.0 *M* HCl. The resulting solution was extracted twice with ether and the combined organic extracts were washed with water and saturated NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to afford the following ketoacid products. The products were isolated pure and used directly in the subsequent reduction step. The physical and spectral data were:

(5*R,6*R**)-(±)-6-(Carboxymethyl)spiro[4.4]nonan-1-one (22a):** 171 mg (0.87 mmol, 87%); IR (thin film) 3300-2500, 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.60-9.80 (bs, 1 H), 2.60 (m, 1 H), 2.30 (m, 3 H), 2.06 (m, 2 H), 1.98 (m, 1 H), 1.83 (m, 2 H), 1.70 (m, 4 H), 1.55 (m, 1 H), 1.31 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 222.8, 178.6, 58.5, 40.8, 37.7, 37.4, 35.6, 32.0, 31.1, 22.7, 19.3; MS (CI, isobutane): *m/e* (%) 196 (27), 179 (100), 155 (21), 137 (27), 97 (48), 80 (57).

(5*R,6*R**)-(±)-1-(Carboxymethyl)spiro[4.5]decan-6-one (22b):** 179 mg (0.85 mmol, 85%); mp 78-79°C; IR ($CHCl_3$) 3420-2510, 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.00-9.80 (bs, 1 H), 2.90 (m, 1 H), 2.40 (m, 3 H), 2.14 (m, 1 H), 1.98 (m, 2 H), 1.84 (m, 1 H), 1.80-1.45 (complex, 8 H), 1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 213.8, 179.3, 58.1, 39.9, 39.1, 35.0, 34.9, 31.6, 29.6, 26.9, 21.7, 21.6; MS (CI, isobutane): *m/e* (%) 210 (10), 193 (100), 169 (16), 151 (34), 111 (31), 80 (28), 67 (32).

(5*R,6*R**)-(±)-1-(Carboxymethyl)spiro[4.6]undecan-6-one (22c):** 197 mg (0.88 mmol, 88%); IR (thin film) 3560-2500, 1720, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00-8.60 (bs, 1 H), 2.56 (m, 4 H), 2.16 (m, 1 H), 1.96 (m, 2 H), 1.88-

1.46 (complex, 11 H), 1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 217.1, 179.0, 60.3, 42.5, 42.3, 36.8, 35.3, 31.0, 30.7, 30.5, 26.2, 25.4, 22.1; MS (CI, isobutane): *m/e* (%) 225 (M+1, 24), 224 (18), 207 (68), 165 (28), 136 (63), 125 (53), 109 (100), 93 (47), 81 (69), 67 (59).

General Procedure for the Sodium Borohydride Reduction of Ketoacids 22a, 22b, and 22c to Afford Hydroxyacids 15a, 15b, and Lactone 24. The general procedure of House and co-workers[76] was followed. A 2-mL ethanol solution of 0.80 mmol of the ketoacid was slowly added to a stirred slurry of 61 mg (1.60 mmol) of sodium borohydride in 3 mL of ethanol at 0°C over the course of 2 min so as to moderate the release of evolved hydrogen gas and the resulting mixture was stirred at room temperature for 6 h. The mixture was then cooled to 0 °C and 2 mL of 1.0 *M* HCl was slowly added dropwise over the course of 5 min, followed by 10 mL of water and enough additional 1.0 *M* HCl to reach a pH of *ca.* 3. The resulting solution was stirred at room temperature for 2 h and extracted twice with ether. The combined organic extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the following reduction products. The physical and spectral data were:

15a: 141 mg (0.71 mmol, 89%); the product isolated was identical spectroscopically to that described previously.

15b: 155 mg (0.73 mmol, 91%); the product isolated was identical spectroscopically to that described previously.

(5*R,6*R**)-(±)-1-(Carboxymethyl)spiro[4.6]undecan-6-ol Lactone (24)**: 141 mg (0.68 mmol, 85%); IR (thin film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.29 (m, 1 H), 2.69 (m, 1 H), 2.34 (m, 1 H), 2.11 (m, 1 H), 2.02-1.79 (complex, 6 H), 1.75-1.42 (complex, 6 H), 1.34 (m, 2 H), 1.19 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 90.0, 46.2, 45.7, 34.0, 32.9, 31.6, 26.9, 26.7, 21.8, 20.9, 20.7, 18.9; MS (EI/DP): *m/e* (%) 208 (12), 166 (50), 148 (100), 95 (32), 81 (46), 67 (65).

General Procedure for Hydrolysis of the Ketoesters 13a and 13b to Afford Ketoacids 23a and 23b. A 1-mL ethanol solution of 0.30 mmol of the ketoester was added to 5 mL of 1.0 *M* NaOH and the resulting solution was heated with stirring at 40 °C for 2 h. The solution was cooled and carefully acidified to a pH of *ca.* 3 by dropwise addition of 6.0 *M* HCl. The resulting solution was extracted twice with ether and the combined organic extracts were washed with water and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The ketoacid products were isolated pure and used directly in the subsequent reduction step. The physical and spectral data were:

(5*R,6*S**)-(±)-6-(Carboxymethyl)spiro[4.4]nonan-1-one (23a):** 53 mg (0.27 mmol, 90%); IR (thin film) 3500-2700, 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00-8.60 (bs, 1 H), 2.46 (m, 1 H), 2.29 (m, 1 H), 2.16 (m, 3 H), 1.91 (m, 2 H), 1.75 (m, 2 H), 1.58 (m, 5 H), 1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 223.0, 179.1, 57.8, 43.9, 39.1, 38.1, 37.0, 35.4, 32.4, 23.3, 19.9; MS (CI, isobutane): *m/e* (%) 196 (31), 179 (100), 137 (30), 97 (65), 80 (70), 67 (30).

(5*R,6*R**)-(±)-1-(Carboxymethyl)spiro[4.5]decan-6-one (23b):** 53 mg (0.25 mmol, 83%); IR (thin film) 3480-2710, 1720, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.00-9.90 (bs, 1 H), 2.59 (m, 1 H), 2.45 (m, 1 H), 2.30 (m, 2 H), 2.12 (m, 3 H), 2.02 (m, 1 H), 1.94-1.58 (complex, 8 H), 1.48 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 214.0, 179.4, 59.3, 44.3, 40.3, 38.1, 36.2, 34.9, 30.3, 26.5, 22.6, 21.4; MS (CI, isobutane): *m/e* (%) 210 (33), 193 (100), 151 (42), 111 (62), 102 (81), 67 (42).

General Procedure for the Sodium Borohydride Reduction of Ketoacids 23a and 23b to Afford Lactones 17a and 17b. The general procedure of House and co-workers[76] was followed. A 1-mL ethanol solution of 0.25 mmol of the ketoacid was slowly added to a stirred slurry of 19 mg (0.50 mmol) of sodium borohydride in 1.5 mL of ethanol at 0°C over the course of 2 min so as to moderate the release of evolved hydrogen gas and the resulting mixture was stirred at room temperature for 6 h. The mixture was then cooled to 0 °C and 0.75 mL of 1.0 *M*

HCl was slowly added dropwise over the course of 5 min, followed by 5 mL of water and enough additional 1.0 *M* HCl to reach a pH of *ca.* 3. The resulting solution was stirred at room temperature for 2 h and extracted twice with ether. The combined organic extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. In both cases, the lactone products were isolated as mixtures of cis diastereomers. The physical and spectral data were:

(5*R,6*S**)-(±)-6-(Carboxymethyl)spiro[4.4]nonan-1-ol Lactone (17a)**: 33 mg (0.18 mmol, 72%); IR (thin film) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (m, 0.5 H), 4.26 (m, 0.5 H), 2.71 (m, 0.5 H), 2.54 (m, 0.5 H), 2.28 (m, 0.5 H), 2.18 (m, 0.5 H), 2.12 (m, 1 H), 2.00 (m, 2 H), 1.83 (m, 2 H), 1.67 (m, 3 H), 1.61 (m, 4 H), 1.05 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.1, 174.3, 87.6, 82.3, 54.0, 41.2, 39.2, 38.1, 37.7, 36.9, 36.0, 34.6, 34.0, 33.9, 30.9, 29.7, 25.9, 25.0, 24.0, 21.3, 19.2; MS (EI/DP): *m/e* (%) 180 (4), 152 (4), 138 (15), 120 (100), 112 (13), 94 (78), 79 (38), 67 (30).

(5*R,6*S**)-(±)-1-(Carboxymethyl)spiro[4.5]decan-6-ol Lactone (17b)**: 36 mg (0.19 mmol, 76%); IR (thin film) 1745, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (m, 0.5 H), 3.96 (m, 0.5 H), 2.69 (m, 0.5 H), 2.61 (m, 0.5 H), 2.52 (m, 1 H), 2.00 (m, 2 H), 1.82-1.26 (complex, 13 H); ^{13}C NMR ($CDCl_3$) δ 174.2, 174.1, 81.9, 79.7, 46.6, 44.7, 44.1, 42.5, 36.8, 35.7, 35.4, 35.1, 34.6, 34.2, 34.0, 29.4, 28.0, 27.1, 25.4, 24.3, 24.1, 22.6, 22.1, 19.5; MS (EI/DP): *m/e* (%) 194 (10), 152 (43), 134 (100), 112 (93), 108 (69), 93 (33), 79 (36), 67 (67).

2,4-DNP of (5*R,6*R**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.6]-undecan-6-one (26)**. To a 5-mL ethanol solution of 2,4-dinitrophenylhydrazine reagent[79] was added a 2-mL ethanol solution of 90 mg (0.36 mmol) of **12c** in one portion and the resulting solution was allowed to stand at room temperature for 4 h until deposition of the adduct was complete. The crude adduct was isolated by filtration and recrystallized from absolute ethanol to afford 130 mg (0.30 mmol, 83 %) of **26** as a fine

orange solid, mp 178-179°C. The spectral data were: IR ($CHCl_3$) 3380, 1725, 1665, 1525, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.29 (s, 1 H), 9.13 (d, 1 H, J = 2.7 Hz), 8.30 (dd, 1 H, J = 9.6, 2.7 Hz), 8.04 (d, 1 H, J = 9.6 Hz), 4.18 (q, 2 H, J = 7.5 Hz), 3.72 (m, 1 H), 2.78 (m, 2 H), 2.46 (m, 1 H), 2.06 (m, 2 H), 1.91-1.54 (complex, 10 H), 1.42 (m, 3 H), 1.30 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6, 165.3, 145.5, 137.6, 130.1, 129.1, 123.5, 116.6, 60.4, 55.2, 42.0, 39.4, 36.0, 33.4, 31.0, 29.4, 28.4, 25.0, 24.5, 20.8, 14.4; HRMS, *m/e* for $C_{21}H_{28}O_6N_4$: calcd, 432.2009; found, 432.2012.

General Procedure for the Preparation of (±)-2-Methoxycarbonyl-2-((*E*)-6-ethoxycarbonyl-5-hexenyl)cycloalkanones (11d, 11e, and 11f). A solution of potassium *tert*-butoxide was generated by dissolving 1.06 g (27.1 mg-atm) of potassium metal in 70 mL of *tert*-butyl alcohol at 40-50°C. The solution was cooled to 20°C and 27.1 mmol of the 2-methoxycarbonylcycloalkanone (**10a**, **10b**, or **10c**) was added with stirring. After stirring for 1 h at 20°C, 7.64 g (27.1 mmol) of ethyl (*E*)-7-iodo-2-heptenoate (**9b**) was added dropwise and the reaction was refluxed for 18 h. The reaction was cooled to 20°C and poured into 125 mL of 0.5 *M* HCl. The resulting solution was extracted twice with ether and the combined ether extracts were washed with 0.5 *M* HCl, water, saturated aqueous $NaHCO_3$, 5% aqueous sodium thiosulfate and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a thick yellow oil. The oil was purified by vacuum distillation using a Kugelrohr apparatus. The physical and spectral properties of the products were the following:

(±)-2-Methoxycarbonyl-2-((*E*)-6-ethoxycarbonyl-5-hexenyl)-cyclopentanone (11d): 5.21 g (17.6 mmol, 65%); bp 140-146°C (0.5 mm Hg); IR (thin film) 1755, 1730, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (dt, 1 H, J = 15.9, 7.0 Hz), 5.83 (d, 1 H, J = 15.9 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.73 (s, 3 H), 2.55 (m, 1 H), 2.40 (m, 1 H), 2.27 (m, 3 H), 1.97 (m, 4 H), 1.53 (m, 3 H), 1.37 (m, 2 H), 1.31 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 214.5, 171.2, 166.4, 148.5, 121.3, 60.2,

59.9, 52.3, 37.7, 33.4, 32.5, 31.6, 28.0, 24.2, 19.4, 14.1; MS (CI, isobutane): *m/e* (%) 297 (M+1, 87), 251 (79), 233 (37), 219 (100), 191 (36).

(±)-2-Methoxycarbonyl-2-((*E*)-6-ethoxycarbonyl-5-hexenyl)-cyclohexanone (11e): 5.21 g (16.8 mmol, 62%); bp 154-158°C (0.5 mm Hg); IR (thin film) 1730, 1720, 1715, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (dt, 1 H, J = 15.6, 6.9 Hz), 5.80 (d, 1 H, J = 15.6 Hz), 4.17 (q, 2 H, J = 7.2 Hz), 3.73 (s, 3 H), 2.43 (m, 3 H), 2.20 (m, 2 H), 2.02 (m, 1 H), 1.87 (m, 1 H), 1.81-1.40 (complex, 7 H), 1.29 (m, 2 H), 1.28 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 207.3, 172.1, 166.2, 148.5, 121.1, 60.5, 59.7, 51.9, 40.7, 35.8, 34.0, 31.5, 28.0, 27.3, 23.5, 22.2, 14.0; MS (CI, isobutane): *m/e* (%) 311 (M+1, 100), 265 (26), 247 (32), 227 (15), 205 (27), 125 (31).

(±)-2-Methoxycarbonyl-2-((*E*)-6-ethoxycarbonyl-5-hexenyl)-cycloheptanone (11f): 6.15 g (19.0 mmol, 70%); bp 162-168°C (0.5 mm Hg); IR (thin film) 1740, 1730, 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 7.2 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 6.9 Hz), 3.72 (s, 3 H), 2.63 (m, 1 H), 2.46 (m, 1 H), 2.17 (m, 3 H), 1.95 (m, 1 H), 1.80-1.36 (complex, 10 H), 1.28 (m, 2 H), 1.27 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 209.2, 172.7, 166.3, 148.5, 121.2, 62.6, 59.8, 51.9, 41.7, 34.8, 32.5, 31.6, 29.6, 28.0, 25.3, 24.6, 23.8, 14.0; MS (CI, isobutane): *m/e* (%) 325 (M+1, 100), 219 (17), 185 (53), 173 (23).

General Decarboxylation-Michael Addition Procedure for the Formation of 6-Ring Spiranes (12d-f and 13d-f). A solution of 5.00 mmol of the (±)-2-methoxycarbonyl-2-((*E*)-6-ethoxycarbonyl-5-hexenyl)cycloalkanone (**11d**, **11e**, or **11f**) and 0.64 g (15.0 mmol) of anhydrous lithium chloride in 15-20 mL of anhydrous HMPA was stirred at 125-130°C for 6 h. The resulting brown reaction mixture was cooled to 25°C, poured into 50 mL of 0.5 *M* HCl and extracted 3x with ether. The combined ether extracts were washed with 0.5 *M* HCl, water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by PTLC using the following elution sequence:

99:1 hexane/ether (2x), 98:2 hexane/ether (2x), 96:4 hexane/ether (3x) and 95:5 hexane/ether (3x). This elution procedure permitted separation of the major and minor diastereomeric products in relatively high purity. In all cases the third band was the minor isomer, the fourth band contained a small amount of a mixture and the fifth band gave the major isomer. The following compounds were isolated:

(5*R,6*R**)-(±)-6-(Ethoxycarbonylmethyl)spiro[4.5]decan-1-one (12d)**: 571mg (2.40 mmol, 48%); IR (thin film) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (q, 2 H, J = 6.9 Hz), 2.36 (m, 1 H), 2.22 (m, 1 H), 2.10 (m, 1 H), 1.98 (m, 2 H), 1.96-1.78 (complex, 5 H), 1.68 (m, 4 H), 1.51 (m, 1 H), 1.30 (m, 2 H), 1.24 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 223.2, 172.4, 60.4, 53.2, 38.6, 37.9, 37.5, 33.3, 28.7, 27.5, 25.5, 21.7, 18.9, 14.2; MS (EI/DP): *m/e* (%) 238 (18), 220 (43), 193 (38), 151 (100), 150 (63), 110 (57), 97 (41), 94 (42), 79 (70), 67 (78). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31. Found: C, 69.97; H, 9.31.

(5*R,6*S**)-(±)-6-(Ethoxycarbonylmethyl)spiro[4.5]decan-1-one (13d)**: 24 mg (0.10 mmol, 2%); IR (thin film) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (q, 2 H, J = 7.2 Hz), 2.56 (m, 1 H), 2.19 (m, 4 H), 2.03 (m, 1 H), 1.87 (m, 2 H), 1.74-1.46 (complex, 6 H), 1.34 (m, 2 H), 1.24 (t, 3 H, J = 7.2 Hz), 1.08 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 222.1, 173.5, 60.3, 50.6, 38.9, 36.4, 36.2, 35.3, 31.8, 27.9, 23.2, 21.6, 18.5, 14.2; MS (EI/DP): *m/e* (%) 238 (23), 220 (38), 193 (32), 150 (100), 108 (61), 97 (49), 79 (68).

(6*R,7*R**)-(±)-7-(Ethoxycarbonylmethyl)spiro[5.5]undecan-1-one (12e)**: 529 mg (2.10 mmol, 42%); IR (thin film) 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (q, 2 H, J = 7.2 Hz), 2.56 (m, 1 H), 2.44 (m, 1 H), 2.28 (m, 2 H), 1.98 (m, 4 H), 1.80-1.38 (complex, 11 H), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 215.0, 173.1, 60.1, 51.5, 38.4, 36.7, 36.3, 32.5, 26.9, 26.8, 26.1, 24.8, 20.7, 20.0, 14.2; MS (EI/DP): *m/e* (%) 252 (17), 234 (46), 207 (39), 165 (100), 111 (61), 98 (84), 97 (58),

79 (69), 67 (77). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.38; H 9.59. Found: C, 70.93; H, 9.64.

(6*R,7*S**)-(±)-7-(Ethoxycarbonylmethyl)spiro[5.5]undecan-1-one (13e)**: 28 mg (0.11 mmol, 2%); IR (thin film) 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (q, 2 H, J = 6.9 Hz), 2.49 (m, 2 H), 2.23 (m, 3 H), 2.01 (m, 2 H), 1.82 (m, 1 H), 1.71-1.37 (complex, 7 H), 1.31 (m, 4 H), 1.21 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 214.5, 173.1, 60.2, 52.3, 37.9, 37.0, 36.3, 35.9, 33.9, 31.2, 28.2, 23.6, 21.4, 19.1, 14.1; MS (EI/DP): *m/e* (%) 252 (19), 234 (48), 207 (38), 165 (100), 164 (73), 110 (59), 97 (61), 79 (72), 67 (79).

(1*R,6*S**)-(±)-1-(Ethoxycarbonylmethyl)spiro[5.6]dodecan-7-one (12f)**: 692 mg (2.60 mmol, 52%); IR (thin film) 1740, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7.2 Hz), 2.60 (m, 1 H), 2.46 (m, 2 H), 2.34 (m, 1 H), 2.00 (m, 1 H), 1.82 (m, 1 H), 1.74-1.36 (complex, 14 H), 1.30 (m, 1 H), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 217.2, 172.8, 60.1, 53.2, 42.4, 38.3, 36.6, 34.9, 31.0, 28.6, 27.2, 25.9, 24.8, 24.6, 20.8, 14.1; MS (EI/DP): *m/e* (%) 266 (21), 220 (45), 179 (79), 150 (83), 112 (74), 96 (66), 81 (100), 79 (67), 67 (81). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.13; H, 9.84. Found: C, 71.93; H, 9.64.

(1*S,6*S**)-(±)-1-(Ethoxycarbonylmethyl)spiro[5.6]dodecan-7-one (13f)**: 27 mg (0.10 mmol, 2%); IR (thin film) 1730, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7.1 Hz), 2.61 (m, 2 H), 2.34 (m, 2 H), 2.21 (m, 1 H), 2.06 (m, 1 H), 1.94-1.48 (complex, 10 H), 1.35 (m, 5 H), 1.20 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 217.3, 173.6, 62.0, 59.9, 45.7, 44.0, 38.1, 37.1, 36.2, 33.3, 30.2, 26.5, 24.9, 23.4, 22.4, 14.2; MS (EI/DP): *m/e* (%) 266 (17), 220 (44), 179 (78), 151 (81), 112 (72), 96 (69), 81 (100), 79 (76), 67 (81).

General Procedure for the Hydrolysis of 12d, 12e, 12f, and 13d to Afford Ketoacids 27d, 27e, 27f, and 31d. A 1-mL ethanol solution of 0.30 mmol of the ketoester was added to 5 mL of 1.0 *M* NaOH and the resulting solution was heated

with stirring at 40 °C for 2 h. The solution was cooled and carefully acidified to a pH of *ca.* 3 by dropwise addition of 6.0 *M* HCl. The resulting solution was extracted twice with ether and the combined organic extracts were washed with water and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the following ketoacid products. The products were isolated pure and used directly in the subsequent reductions and amide formation steps. The physical and spectral data were:

(5*R,6*R**)-(±)-6-(Carboxymethyl)spiro[4.5]decan-1-one (27d)**: 53 mg (0.25 mmol, 83%); IR (thin film) 3460-2700, 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.30-9.80 (bs, 1 H), 2.40 (m, 1 H), 2.22 (m, 1 H), 2.10 (m, 2 H), 1.98-1.80 (complex, 8 H), 1.54 (m, 1 H), 1.31 (m, 3 H), 1.08 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 223.4, 178.3, 53.2, 38.4, 37.5, 37.1, 33.0, 28.6, 27.4, 25.4, 21.5, 18.8; MS (CI, isobutane): *m/e* (%) 210 (25), 193 (100), 169 (36), 151 (42), 111 (55), 67 (38).

(6*R,7*R**)-(±)-7-(Carboxymethyl)spiro[5.5]undecan-1-one (27e)**: 57 mg (0.26 mmol, 87%); IR (thin film) 3500-2720, 1720, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.80-10.20 (bs, 1 H), 2.46 (m, 2 H), 2.24 (m, 2 H), 1.95 (m, 5 H), 1.76-1.24 (complex, 9 H), 1.08 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 215.5, 179.1, 51.5, 38.3, 36.7, 36.2, 32.4, 27.3, 26.8, 24.9, 20.6, 20.0; MS (CI, isobutane): *m/e* (%) 224 (18), 207 (100), 183 (29), 164 (53), 125 (45), 67 (40).

(1*R,6*S**)-(±)-1-(Carboxymethyl)spiro[5.6]dodecan-7-one (27f)**: 67 mg (0.28 mmol, 93%); IR (thin film) 3620-2870, 1725, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.30-9.85 (bs, 1 H), 2.54 (m, 1 H), 2.38 (m, 3 H), 1.97 (m, 1 H), 1.80 (m, 1 H), 1.71-1.13 (complex, 15 H); ^{13}C NMR ($CDCl_3$) δ 217.5, 179.1, 53.3, 42.2, 38.0, 36.5, 35.3, 31.0, 28.7, 27.3, 25.9, 25.0, 24.6, 20.8; MS (CI, isobutane): *m/e* (%) 238 (31), 221 (76), 179 (33), 150 (65), 139 (51), 123 (100), 81 (67), 67 (62).

(5*R,6*S**)-(±)-6-(Carboxymethyl)spiro[4.5]decan-1-one (31d)**: 55 mg (0.26 mmol, 87%); IR (thin film) 3770-2810, 1745, 1715 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 10.21-9.62 (bs, 1 H), 2.63 (m, 1 H), 2.22 (m, 2 H), 2.01 (m, 1 H), 1.87 (m, 2 H), 1.65 (m, 2 H), 1.45 (m, 2 H), 1.32-1.09 (complex, 6 H), 0.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 224.1, 178.6, 50.6, 38.9, 36.2 (2), 34.9, 31.7, 29.7, 27.9, 23.1, 21.6, 18.5; MS (CI, isobutane): *m/e* (%) 210 (31), 193 (100), 171 (25), 169 (42), 151 (53), 111 (55), 79 (37), 67 (42).

General Procedure for the Preparation of Amides 29a and 29c. The general procedure of Meinwald and co-workers[80] was followed. A 5-mL benzene solution of 1.00 mmol of the ketoacid (**27d** or **27f**) and 570 mg (4.50 mmol, 0.40 mL) of oxalyl chloride was refluxed with stirring for 2 h and the resulting solution was allowed to cool to room temperature. The benzene and excess oxalyl chloride were removed by rotory evaporation to afford a light yellow residue which was dissolved in 5 mL of dry benzene. The benzene solution was then added dropwise to a stirred 10-mL benzene solution of 120 mg (1.5 mmol) of dry pyridine and 200 mg (1.2 mmol) of 4-bromoaniline at 0-5°C and the resulting mixture was stirred at room temperature for 6 h. The mixture was concentrated *in vacuo* to afford a yellow residue which was dissolved in water and extracted twice with ether. The combined organic extracts were washed with 1.0 *M* HCl, water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a light yellow solid that was recrystallized from ether / hexane to afford the amide product. The physical and spectral properties were:

(5*R,6*R**)-(±)-*N*-(4-Bromophenyl)-6-(carbamoylmethyl)spiro[4.5]-decan-1-one (29a)**: 320 mg (0.88 mmol, 88%); mp 155-156°C; IR ($CHCl_3$) 3320, 1745, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (bs, 1 H), 7.36 (m, 4 H), 2.44 (m, 1 H), 2.13 (m, 2 H), 2.06-1.83 (m, 7 H), 1.64 (m, 3 H), 1.24 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 225.1, 170.6, 137.3, 131.9, 121.2, 116.5, 54.5, 41.8, 39.5, 38.2, 32.7, 29.0, 26.9, 25.6, 21.4, 18.6; HRMS, *m/e* for $C_{18}H_{22}O_2N^{79}Br$: calcd, 363.0834; found, 363.0832.

(1*R,6*S**)-(±)-N-(4-Bromophenyl)-1-(carbamoylmethyl)spiro[5.6]-dodecan-7-one (29c)**: 356 mg (0.91 mmol, 91%); mp 183-184°C; IR ($CHCl_3$) 3325, 1715, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24 (bs, 1 H), 7.50 (m, 2 H), 7.41 (m, 2 H), 2.77 (m, 1 H), 2.42 (m, 2 H), 2.29 (m, 1 H), 2.04 (m, 1 H), 1.80 (m, 7 H), 1.61-1.14 (complex, 9 H); ^{13}C NMR ($CDCl_3$) δ 219.1, 171.7, 137.7, 131.8, 121.0, 116.1, 54.2, 42.2, 41.7, 40.3, 37.5, 31.1, 28.4, 27.9, 26.1, 26.0, 25.4, 20.8; HRMS, *m/e* for $C_{20}H_{26}O_2N^{79}Br$: calcd, 391.1147; found, 391.1148.

General Procedure for the Sodium Borohydride Reduction of Ketoacids 27d, 27e, and 31d to Afford Hydroxyacids 30d and 30e and Lactone 32d. The general procedure of House and co-workers[76] was followed. A 1-mL ethanol solution of 0.25 mmol of the ketoacid was slowly added to a stirred slurry of 19 mg (0.50 mmol) of sodium borohydride in 1.5 mL of ethanol at 0°C over the course of 2 min so as to moderate the release of evolved hydrogen gas and the resulting mixture was stirred at room temperature for 6 h. The mixture was then cooled to 0 °C and 0.75 mL of 1.0 *M* HCl was slowly added dropwise over the course of 5 min, followed by 5 mL of water and enough additional 1.0 *M* HCl to reach a pH of *ca.* 3. The resulting solution was stirred at room temperature for 2 h and extracted twice with ether. The combined organic extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the following reduction products. The physical and spectral data were:

(5*R,6*R**)-(±)-6-(Carboxymethyl)spiro[4.5]decan-1-ol (30d)**: 45 mg (0.21 mmol, 84%); IR (thin film) 3530-2710, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55-5.92 (bs, 2 H), 3.51 (m, 1 H), 2.65 (m, 1 H), 2.27 (m, 2 H), 1.96 (m, 1 H), 1.79 (m, 5 H), 1.53 (m, 2 H), 1.31 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 179.3, 72.8, 45.6, 35.7, 34.2, 29.5, 28.9, 26.1, 24.2, 23.9, 21.2, 20.6; HRMS, *m/e* for $C_{12}H_{20}O_3$: calcd, 212.1412; found, 212.1416.

(6*R,7*R**)-(±)-7-(Carboxymethyl)spiro[5.5]undecan-1-ol (30e):** 48 mg (0.21 mmol, 84%); mp 136-137°C; IR($CHCl_3$) 3450-2700, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40-5.80 (bs, 2 H), 3.48 (m, 1 H), 2.62 (m, 1 H), 2.19 (m, 1 H), 1.95 (m, 1 H), 1.86 (m, 4 H), 1.55 (m, 2 H), 1.34 (m, 7 H), 0.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 179.6, 72.6, 40.8, 36.9, 35.0, 28.7, 28.6 (2), 26.3, 24.8, 24.7, 20.4, 19.9; HRMS, *m/e* for $C_{13}H_{22}O_3$: calcd, 226.1569; found, 226.1569.

(5*R,6*S**)-(±)-6-(Carboxymethyl)spiro[4.5]decan-1-ol Lactone (32d):** 43 mg (0.22 mmol, 88%); IR (thin film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37 (m, 1 H), 2.43 (m, 1 H), 2.19 (m, 1 H), 1.89 (m, 2 H), 1.80-1.42 (complex, 10 H), 1.25 (m, 2 H), 1.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 93.0, 44.8, 36.5, 35.5, 33.2, 31.5, 29.2, 25.8, 25.5, 22.2, 21.7; HRMS, *m/e* for $C_{12}H_{18}O_2$: calcd, 194.1307; found, 194.1313.

Single Crystal X-ray Structure Determination of the 2,4-DNP of (5*R,6*R**)-(±)-1-(Ethoxycarbonylmethyl)spiro[4.6]undecan-6-one (26).** A crystal of $C_{21}H_{28}N_4O_6$, grown from absolute ethanol, was mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (see Table XII) were determined by least squares refinement of the best angular positions for fifteen independent reflections (2θ>15°) during normal alignment procedures using molybdenum radiation (λ=0.71069 Å). Data (1493 independent points after removal of redundant data) were collected at room temperature using a variable scan rate, a θ-2θ scan mode and and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 45°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections. As the intensities of these reflections showed less than 5% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization and background effects. Observed reflections [780 ((I>3.0σ(I))] were used for solution of non-hydrogen atom positions by direct methods using SHELX86.[81] Refinement[64] of

TABLE XII

CRYSTAL DATA FOR **26**

Formula	$C_{21}H_{28}N_4O_6$
MWT	432.5
a	16.317(12) Å
b	18.805(14)
c	7.140(2)
α	90°
β	90.0
γ	90.0
V	2191.9(2) $Å^3$
F(000)	920
μMoK_α	0.909 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.311 g cm^{-3}
Z	4
Space Group	$Pc2_1n$
Obs. refl.	780
Octants meas.	+h, +k, +1
R/Rw	7.0/8.9%
G.O.F.	0.447

scale factor, positional and anisotropic thermal parameters for all non-hydrogen atoms were carried out to convergence. The atoms of the side chain attached at C1 showed disorder. The disorder was not entirely resolved by assignment of two partially occupied positions to atoms C13-C15 and O1 and O2 of the side chain ethyl ester group. The positions of 20 hydrogen atoms not associated with side chain atoms were located from a difference Fourier synthesis and were included in the final cycles of refinement with fixed, isotropic thermal parameters. The final cycle of refinement [function minimized, $\Sigma(|Fo|-|Fc|)^2$] led to a final agreement factor, R=7.0%. [$R=(\Sigma||Fo|-|Fc||/\Sigma w|Fo|) \times 100$]. Scattering factors were taken from Cromer and Mann.[65] In the final stages of refinement a weight factor of $1/\sigma(F)2$ was used. R_w=8.9%. Tables XVII-XIX in Appendix B list bond angles and distances, positional parameters, and final anisotropic thermal parameters for **26**.

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APPENDIX A

TABLES OF CRYSTALLOGRAPHIC DATA FOR (1*R**,3a*S**,7a*S**)-(±)-1-(CARBOXYMETHYL)-1, 3, 3a, 4,5, 6, 7, 7a-OCTAHYDRO-BENZO[c]THIOPHENE (**114**)

TABLE XIII

BOND ANGLES AND DISTANCES FOR (1*R**,3a*S**,7a*S**)-(±)-1-(CARBOXYMETHYL)-1, 3, 3a, 4,5, 6, 7, 7a-OCTAHYDRO-BENZO[c]THIOPHENE (**114**)

Atoms	Distance (Å)	Atoms	Angle (°)
C1 - S2	1.831(4)	C7a - C1 - S2	106.5(3)
C1 - C7a	1.544(7)	C7a - C1 - C8	110.9(4)
S2 - C3	1.824(6)	S2 - C1 - C8	112.6(3)
C3 - C3a	1.518(6)	C1 - S2 - C3	93.8(2)
C3a - C4	1.539(7)	S2 - C3 - C3a	105.6(3)
C3a - C7a	1.530(6)	C3 - C3a - C7a	104.8(9)
C4 - C5	1.517(7)	C3 - C3a - C4	113.1(4)
C5 - C6	1.522(7)	C4 - C3a - C7a	111.9(3)
C6 - C7	1.533(7)	C3a - C4 - C5	111.3(4)
C7 - C7a	1.530(6)	C4 - C5 - C6	110.6(4)
C1 - C8	1.511(7)	C5 - C6 - C7	111.5(4)
C8 - C9	1.503(8)	C6 - C7 - C7a	113.0(3)
C9 - O1	1.235(6)	C7 - C7a - C1	113.2(3)
C9 - O2	1.293(6)	C7 - C7a - C3a	113.0(4)
		C1 - C7a - C3a	108.9(3)
		C1 - C8 - C9	115.5(4)
		C8 - C9 - O1	122.9(5)
		C8 - C9 - O2	113.6(4)
		O1 - C9 - O2	123.4(5)

TABLE XIV

DIHEDRAL ANGLES FOR (1*R**,3a*S**,7a*S**)-(±)-1-(CARBOXYMETHYL)-1,3,3a,4,5,6,7,7a-OCTAHYDROBENZO[c]THIOPHENE (**114**)

Atoms	Dihedral Angle (°)
H7a-C7a-C1-H1	-151.8(3)
H7a-C7a-C3a-H3a	58.4(5)
H3a-C3a-C3-H31	-42.0(5)
H3a-C3a-C3-H32	74.4(5)

TABLE XV

POSITIONAL PARAMETERS FOR (1*R**,3a*S**,7a*S**)-(±)-1-(CARBOXYMETHYL)-1, 3, 3a, 4,5, 6, 7, 7a-OCTAHYDROBENZO[c]THIOPHENE (**114**)

Atoms	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
S2	0.4599(1)	0.0850(3)	0.8050(1)
O1	0.4377(3)	-0.0876(7)	0.5774(3)
O2	0.4330(2)	0.2847(7)	0.5010(3)
C1	0.3402(3)	0.1201(8)	0.7065(3)
C3	0.4264(3)	0.2640(10)	0.8999(4)
C3A	0.3176(3)	0.2306(8)	0.8712(3)
C4	0.2891(3)	-0.0290(9)	0.9024(3)
C5	0.1801(3)	-0.0677(9)	0.8604(4)
C6	0.1423(3)	-0.0467(9)	0.7445(4)
C7	0.1690(3)	0.2086(10)	0.7089(3)
C7A	0.2772(3)	0.2699(8)	0.7556(3)
C8	0.3447(3)	0.2535(9)	0.6123(3)
C9	0.4102(3)	0.1345(9)	0.5625(3)
H1	0.3088	-0.0580	0.6871
H2	0.4800	0.1906	0.4688
H31	0.4421	0.4555	0.8960
H32	0.4682	0.2134	0.9752
H3A1	0.2884	0.3844	0.9078
H41	0.3182	-0.0146	0.9857
H42	0.3263	-0.1663	0.8798
H51	0.1543	-0.2601	0.8766
H52	0.1435	0.0725	0.8987
H61	0.0618	-0.0945	0.7079
H62	0.1753	-0.1975	0.7167
H71	0.1488	0.2289	0.6295
H72	0.1315	0.2505	0.7345
H7A1	0.2871	0.4642	0.7391
H81	0.2775	0.2784	0.5387
H82	0.3675	0.4346	0.6179

TABLE XVI

ANISOTROPIC THERMAL PARAMETERS FOR (1*R**,3a*S**,7a*S**)-(±)-1-(CARBOXYMETHYL)-1, 3, 3a, 4,5, 6, 7, 7a-OCTAHYDROBENZO[c]THIOPHENE (**114**)

Atom	U11	U22	U33	U12	U13	U23
S2	344(7)	742(10)	538(8)	79(6)	170(6)	42(8)
O1	79(2)	45(2)	67(2)	13(2)	52(2)	7(2)
O2	85(2)	59(2)	67(2)	15(2)	57(2)	19(2)
C1	32(2)	32(2)	34(2)	0(2)	14(2)	4(2)
C3	45(2)	51(3)	49(3)	-7(2)	6(2)	-3(2)
C3A	46(2)	33(2)	38(2)	2(2)	18(2)	-4(2)
C4	55(3)	50(3)	37(2)	5(2)	20(2)	2(2)
C5	55(3)	46(3)	57(3)	-7(2)	33(2)	7(2)
C6	39(2)	41(2)	53(3)	-6(2)	18(2)	-4(2)
C7	36(2)	53(3)	43(2)	9(2)	20(2)	7(2)
C7A	38(2)	27(2)	41(2)	5(2)	20(2)	1(2)
C8	54(2)	42(3)	43(2)	7(2)	28(2)	11(2)
C9	39(2)	47(3)	35(2)	2(2)	18(2)	4(2)

Anisotropic thermal parameters in the format:

$\exp[-2\pi^2(U11h2a^{*2} + U22k2b^{*2} + U3312c^{*2} + 2U12hka^*b^* + 2U13hla^*c^* + 2U23klb^*c^*)]$

x 10^3 for C, O; x 10^4 for S

APPENDIX B

TABLES OF CRYSTALLOGRAPHIC DATA FOR THE 2,4-DNP OF (5*R**, 6*R**)-(±)-1-(ETHOXYCARBONYLMETHYL)SPIRO[4.6]UNDECAN-6-ONE (**26**)

TABLE XVII

BOND ANGLES AND DISTANCES FOR THE 2,4-DNP OF (5*R**, 6*R**)-(±)-1-(ETHOXYCARBONYLMETHYL)-SPIRO[4.6]UNDECAN-6-ONE (**26**)

Atoms	Distance (Å)	Atoms	Angle (°)
C1 - C2	1.50(3)	C2 - C1 - C5	100(1)
C1- C5	1.56(2)	C2 - C1 - C12	118(2)
C1 - C12	1.55(2)	C5 - C1 - C12	115(2)
C2 - C3	1.48(3)	C1 - C2 - C3	108(2)
C3 - C4	1.48(3)	C2 - C3 - C4	106(2)
C4 - C5	1.55(3)	C3 - C4 - C5	106(2)
C5 - C6	1.53(2)	C1 - C5 - C4	101(1)
C5 - C11	1.53(2)	C1 - C5 - C6	114(1)
C6 - C7	1.49(2)	C1 - C5 - C11	112(2)
C6 - N1	1.30(2)	C4 - C5 - C6	109(1)
C7 - C8	1.49(3)	C4 - C5 - C11	114(1)
C8 - C9	1.56(3)	C6 - C5 - C11	108(2)
C9 - C10	1.56(4)	C5 - C6 - N1	116(2)
C10 - C11	1.51(3)	C5 - C6 - C7	120(1)
N1- N2	1.39(2)	N1 - C6 - C7	124(2)
N2 - C16	1.36(2)	C6 - C7 - C8	111(2)
C16 - C17	1.46(2)	C7 - C8 - C9	115(2)
C16 - C21	1.43(2)	C8 - C9 - C10	112(2)
C17 - C18	1.36(3)	C9 - C10 - C11	115(2)
C17 - N3	1.43(3)	C10 - C11 - C5	120(2)
N3 - O3	1.24(2)	C6 - N1 - N2	116(1)
N3 - O4	1.23(2)	N1 - N2 - C16	117(1)
C18 - C19	1.36(2)	N2 - C16 - C17	122(2)
C19 - C20	1.37(2)	N2 - C16 - C21	123(2)
C19 - N4	1.45(2)	C17 - C16 - C21	114(2)
N4 - O5	1.24(2)	C16 - C17 - N3	121(2)
N4 - O6	1.18(2)	C16 - C17 - C18	119(2)
C20 - C21	1.34(2)	N3 - C17 - C18	120(2)

TABLE XVII (Continued)

Atoms	Distance (Å)	Atoms	Angle (°)
		N4 - C19 - C20	119(2)
		C19 - N4 - O5	119(1)
		C19 - N4 - O6	119(2)
		O5 - N4 - O6	123(1)
		C19 - C20 - C21	119(2)
		C20 - C21 - C16	124(2)
		C17 - N3 - O3	121(2)
		C17 - N3 - O4	116(2)
		C17 - C18 - C19	123(2)
		C18 - C19 - C20	121(2)
		C18 - C19 - N4	120(2)

TABLE XVIII

POSITIONAL PARAMETERS FOR THE 2,4-DNP OF (5*R**, 6*R**)-(±)-1-(ETHOXYCARBONYLMETHYL)SPIRO-[4.6]UNDECAN-6-ONE (**26**)

Atom	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
O3	0.0950(8)	0.2665(8)	0.2365(20)
O4	0.2147(8)	0.3145(8)	0.1973(25)
O5	0.4625(8)	0.1969(8)	0.3213(20)
O6	0.4618(8)	0.0890(8)	0.4091(17)
N1	0.0462(8)	0.0688(8)	0.3749(18)
N2	0.0825(8)	0.1345(9)	0.3453(21)
N3	0.1709(12)	0.2640(10)	0.2422(21)
N4	0.4266(8)	0.1411(9)	0.3641(24)
C1	-0.0110(12)	-0.0666(10)	0.4357(26)
C2	-0.0532(12)	-0.1320(11)	0.3648(30)
C3	-0.0898(12)	-0.1158(12)	0.1800(27)
C4	-0.0920(11)	-0.0375(12)	0.1656(28)
C5	-0.0714(9)	-0.0085(9)	0.3636(25)
C6	-0.0320(10)	0.0650(10)	0.3432(22)
C7	-0.0832(10)	0.1274(11)	0.2889(25)
C8	-0.1099(12)	0.1684(12)	0.4569(35)
C9	-0.1754(14)	0.1305(15)	0.5810(32)
C10	-0.1476(12)	0.0550(13)	0.6437(30)
C11	-0.1463(11)	-0.0004(13)	0.4902(29)
C12	0.0089(10)	-0.0623(10)	0.6482(24)
C16	0.1660(10)	0.1363(10)	0.3465(21)
C17	0.2121(12)	0.2008(10)	0.3009(22)
C18	0.2957(11)	0.1989(9)	0.3078(24)
C19	0.3378(9)	0.1394(10)	0.3560(23)
C20	0.2980(9)	0.0786(10)	0.4075(20)
C21	0.2160(11)	0.0767(10)	0.3985(22)
O1A	0.1269(16)	-0.1346(15)	0.5700(37)
O1B	0.1378(21)	-0.0988(21)	0.6256(51)
O2A	0.0841(16)	-0.1215(17)	0.8773(42)
O2B	0.1031(19)	-0.0998(18)	0.8922(41)
C13	0.0853(12)	-0.1057(11)	0.7081(46)
C14A	0.1651(16)	-0.1418(19)	0.9565(49)
C14B	0.1449(36)	-0.2010(24)	0.9907(84)
C15	0.1542(33)	-0.2023(29)	1.0979(52)

TABLE XVIII (Continued)

Atom	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
H1	0.0401	-0.0612	0.3686
H21	-0.0960	-0.1479	0.4497
H22	-0.0134	-0.1714	0.3511
H31	-0.1447	-0.1389	0.1706
H32	-0.0563	-0.1386	0.0791
H41	-0.1477	-0.0196	0.1272
H42	-0.0537	-0.0182	0.0722
H71	-0.0539	0.1599	0.2021
H72	-0.1340	0.1130	0.2232
H81	-0.0598	0.1784	0.5354
H82	-0.1300	0.2171	0.4209
H91	-0.1821	0.1631	0.6904
H92	-0.2231	0.1313	0.5075
H101	-0.0901	0.0563	0.6920
H102	-0.1823	0.0391	0.7441
H111	-0.1578	-0.0466	0.5508
H112	-0.1945	0.0106	0.4113
H18	0.3280	0.2421	0.2712
H20	0.3301	0.0363	0.4474
H21	0.1871	0.0309	0.4313

TABLE XIX

ANISOTROPIC THERMAL PARAMETERS FOR THE 2,4-DNP OF (5*R**, 6*R**)-(±)-1-(ETHOXYCARBONYLMETHYL)-SPIRO[4.6]UNDECAN-6-ONE (**26**)

Atom	U11	U22	U33	U12	U13	U23
O3	56(8)	61(8)	109(10)	12(8)	-13(8)	15(8)
O4	82(10)	62(9)	150(14)	-16(8)	-13(10)	34(10)
O5	59(8)	93(11)	145(13)	-8(8)	0(9)	-14(11)
O6	58(8)	87(10)	81(9)	-6(7)	0(7)	-8(9)
N1	44(8)	63(10)	51(9)	-18(8)	-4(7)	-7(9)
N2	37(8)	64(10)	66(10)	-11(8)	5(8)	-2(9)
N3	96(13)	41(9)	51(9)	1(11)	-23(9)	16(8)
N4	53(9)	67(9)	82(10)	0(9)	-7(9)	-25(9)
C1	70(14)	39(10)	69(13)	-17(11)	3(11)	-12(10)
C2	79(14)	74(16)	74(16)	-11(12)	27(12)	23(13)
C3	81(14)	93(18)	64(14)	-29(12)	6(12)	0(13)
C4	49(13)	91(15)	71(15)	-24(11)	-20(11)	13(13)
C5	28(9)	50(11)	67(12)	-12(9)	6(9)	14(11)
C6	55(11)	68(11)	31(9)	12(11)	6(9)	0(9)
C7	26(9)	81(14)	62(12)	10(9)	2(9)	-4(11)
C8	58(13)	87(16)	105(19)	23(14)	-15(14)	11(15)
C9	109(17)	117(19)	68(16)	48(16)	-8(13)	-9(15)
C10	57(12)	113(19)	64(14)	8(13)	23(11)	-1(15)
C11	53(10)	89(15)	79(16)	-14(11)	-23(12)	35(14)
C12	66(11)	56(11)	43(10)	0(9)	-14(9)	21(9)
C16	59(11)	43(9)	15(8)	15(10)	-8(9)	6(7)
C17	69(12)	38(11)	24(10)	-4(11)	-1(9)	14(8)
C18	51(13)	42(10)	62(13)	-12(10)	-5(11)	0(9)
C19	45(9)	66(10)	31(9)	-13(9)	1(9)	-11(9)
C20	22(10)	69(13)	41(10)	5(9)	-11(7)	-8(9)
C21	61(13)	34(12)	42(11)	-17(10)	0(9)	-5(10)
C13	44(15)	59(14)	172(26)	-20(11)	-14(17)	15(17)
O1A	5(0)	75(18)	125(24)	58(16)	55(18)	-26(14)
O1B	5(0)	93(21)	114(30)	55(25)	-15(21)	-18(19)
O2A	5(0)	13(17)	67(23)	28(16)	-26(15)	-18(15)
O2B	5(0)	52(21)	55(21)	42(19)	-12(17)	-46(18)
C14A	121(21)	140(26)	192(30)	7(21)	-25(20)	63(24)
C14B	5(-0)	108(37)	31(25)	102(45)	22(24)	-24(41)
C15	5(0)	81(30)	90(33)	21(23)	-5(24)	-18(26)

VITA

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