TANDEM REACTIONS FOR THE SYNTHESIS OF SUBSTITUTED TETRAHYDROQUINOLINE-4- CARBOXYLIC ESTERS AND RACEMIC AND CHIRAL SUBSTITUTED BENZAZEPINE-5-CARBOXYLIC ESTERS

By

LARA BETH JOHNSON

Bachelor of Science

Oral Roberts University

Tulsa, Oklahoma

1997

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
December, 2003

TANDEM REACTIONS FOR THE SYNTHESIS OF SUBSTITUTED TETRAHYDROQUINOLINE-4-CARBOXYLIC ESTERS AND RACEMIC AND CHIRAL SUBSTITUTED BENZAZEPINE-5-CARBOXYLIC ESTERS

Thesis Approved:

Richard A. Bunce
(Thesis Advisor)

K. D. Berlin

Andrew Mort

Warren T Ford

M. Nichols

Alfred Larkin
(Dean of the Graduate College)

PREFACE

A tandem reduction-reductive amination sequence has been developed for the synthesis of benzo-fused substituted nitrogen heterocycles, including 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters as well as 2-alkyl-1*H*-1-benzazepine-5-carboxylic esters. The key step in the synthesis is a tandem reduction-reductive amination sequence involving (1) catalytic reduction of an aromatic nitro group followed by (2) reductive amination with an intramolecular ketone or aldehyde substituent. In substrates incorporating a ketone group, reduction of the final imine intermediate was highly diastereoselective, giving predominantly the product having a cis relationship between the substituents at the C2 and C4 or C2 and C5 positions.

This tandem reduction-reductive amination sequence has been extended to the enantioselective synthesis of 2-alkyl-1*H*-1-benzazepine-5-carboxylic esters using (-)-8-phenylmenthol as a chiral auxiliary. The key step in the synthesis was the diastereoselective conjugate addition reaction of (-)-8-phenylmenthyl (2-nitrophenyl)acetate with α,β-unsaturated ketones. The diastereoselectivities of the conjugate additions were moderate as a result of the reaction conditions. Reduction of the (-)-8-phenylmenthyl ester and isolation of pure (-)-8-phenylmenthol demonstrated that the chiral auxiliary can be recycled.

ACKNOWLEGEMENTS

I would like to express much thanks to Dr. R. A. Bunce, my research advisor and the chairman of my graduate committee, for his guidance of my graduate work. His instruction in both organic theory and laboratory technique were invaluable to my graduate experience. I would also like to thank Drs. K. D. Berlin, E. M. Holt, A. W. Apblett, and A. J. Mort for agreeing to be on my graduate committee.

Thanks are also due to Drs. E. M. Holt and R. Hallford for their assistance with the X-ray crystallographic studies of some of the compounds synthesized during the course of my graduate work.

I also thank Dr. S. V. Kotturi, a fellow graduate student in Dr. Bunce's research group, for his assistance on some of my experiments. Thank you also to Jason Lewis, Derrick Herron, Matthew Ackerman, and Lu Hale for helping make the laboratory a more pleasant place to work.

I would like to thank the Department of Chemistry for providing a teaching assistantship to me during my studies at OSU. Thanks also to Carolyn, Glenda, and Cheryl in the Chemistry Department office for their assistance over the years.

TABLE OF CONTENTS

Chapter Page

Chapter Page

LIST OF TABLES

LIST OF FIGURES

Figure Page

LIST OF PLATES

CHAPTER I

REDUCTIVE CYCLIZATION OF AROMATIC AND ALIPHATIC NITRO COMPOUNDS CONTAINING AN INTRAMOLECULAR CARBONYL GROUP

Introduction

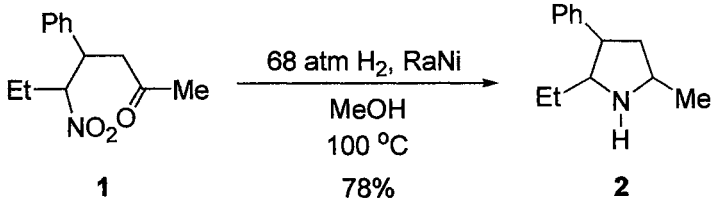
Nitro groups are easily hydrogenated to the corresponding amines or the hydroxylamines. Rylander[1] has reviewed catalytic hydrogenation methods for reducing aromatic and aliphatic nitro groups. The catalysts used for the reduction of nitro compounds include supported and unsupported palladium, platinum, and nickel, as well as rhodium and ruthenium. The reaction of the products of reduced nitro groups, i.e. amines and hydroxylamines, with other functional groups present in the molecule provides a convenient means of synthesizing various nitrogen heterocycles. The product of the cyclization depends on the functional group that reacts with the reduced nitro and can include lactams, *N*-hydroxylactams, as well as saturated and unsaturated nitrogen heterocycles.

In the present work, the reduction of an aromatic nitro group followed by cyclization with an aldehyde, ketone, or ester functional group present in the molecule resulted in cyclization to a nitrogen heterocycle. This process is termed a tandem reduction-reductive amination. With respect to other groups in the molecule, the

reduction-reductive amination of the aromatic nitro group with an intramolecular ketone occurred with a high degree of diastereoselectivity.

Early Examples

In 1948, Kloetzel[2] reported the catalytic hydrogenation of γ-nitroketones in the synthesis of substituted pyrrolidines. For example, the catalytic hydrogenation of **1** under 68 atm hydrogen with a Raney nickel catalyst in methanol at 100 °C yielded **2** in 78% yield (Figure 1). The product yields were increased by the addition of liquid ammonia to the hydrogenation vessel.



1 **2**

Figure 1. Catalytic hydrogenation of γ-nitroketone **1**.

Another early example involved the catalytic hydrogenation of 2-nitro-4,5-dimethoxyphenylacetic acid (**3**) under 3 atm of hydrogen with an 8% palladium-on-carbon catalyst in acetic acid at 80 °C. This resulted in the formation of 2-indolinone **4** in 75% yield (Figure 2).[3] Acidic conditions and higher temperatures were necessary for lactam cyclization to occur. Catalytic hydrogenation of ethyl ester **5** carried out in ethyl acetate at room temperature gave uncyclized aminoester **6**.

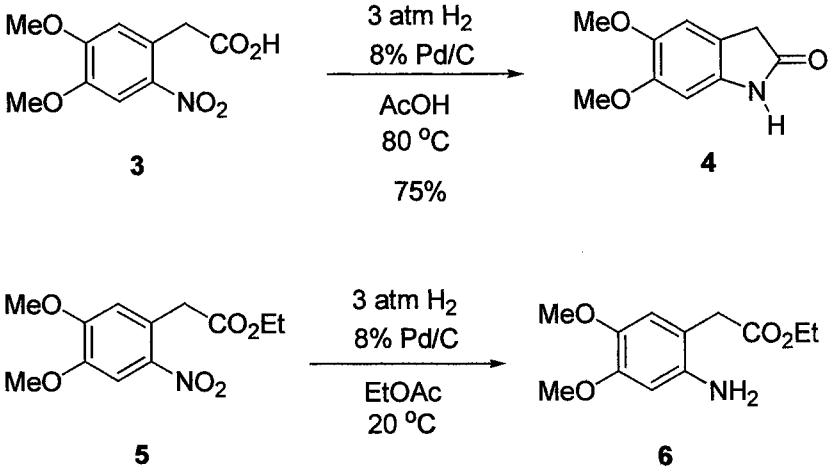


Figure 2. Reductive cyclization of nitroacid **3** and reduction of nitroester **5**.

Masamune and co-workers[4] used a reductive cyclization of nitroacids in the preparation of octahydrophenanthridines. Catalytic hydrogenation of **7** under 1 atm of hydrogen in ethyl acetate in the presence of platinum oxide at 20 °C produced **8** (Figure 3). Reduction of ester **9** under the same conditions also produced **8**.

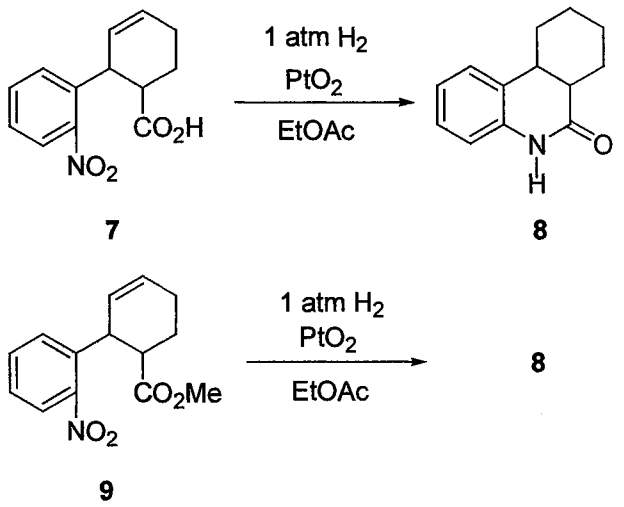
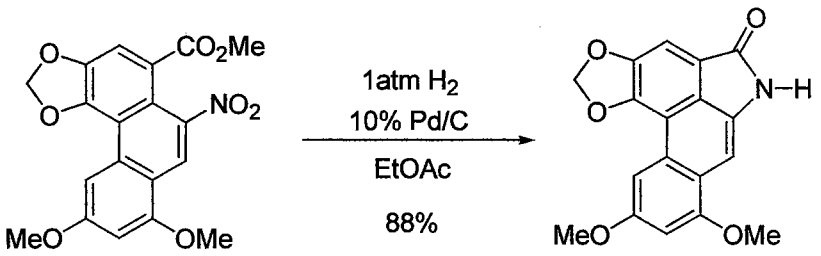


Figure 3. Reductive cyclization of nitroacid **7** and nitroester **9** producing cyclized product **8.**

Synthesis of Lactams

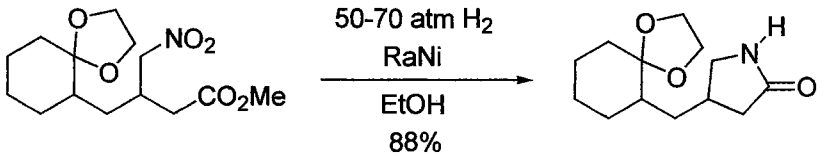
Kupchan and co-workers[5] utilized the reductive cyclization of a nitroester in the structure elucidation of aristolochic acid derivatives. The aristolochic acid derivatives were being studied for their potential use as tumor inhibitors. The methyl ester of aristolochic acid **10** was catalytically hydrogenated at atmospheric pressure using 10% palladium-on-carbon in ethyl acetate at 20 °C to produce **11** in 88% yield (Figure 4).



10 **11**

Figure 4. Catalytic hydrogenation of nitroester **10** to yield a lactam.

Gutsche and co-workers[6] also successfully reduced a nitroester to produce a lactam. Catalytic hydrogenation of nitroester **12** under 50-70 atm hydrogen using Raney nickel in ethanol at 80-100 °C produced lactam **13** in 88% yield (Figure 5).



12 **13**

Figure 5. Catalytic hydrogenation of nitroester **12** to yield a lactam.

Cyclizations Involving *N*-Hydroxyl Amines

Mann and co-workers[7] have demonstrated that partial reduction of a nitro group to a hydroxylamine followed by cyclization with an intramolecular carboxyl group resulted in the formation of *N*-hydroxylactam products (Figure 6). Reductive cyclization of **14** in ethanol under 1 atm hydrogen with a platinum oxide catalyst at 20 °C produced *N*-hydroxylactam **15** in 90% yield. Treatment of the same nitro ester **14** with tin(II) chloride in concentrated hydrochloric acid produced lactam **16** in 80% yield. Reduction of a similar nitroester, **17**, using catalytic hydrogentation with a platinum oxide catalyst or tin(II) chloride resulted in formation of lactam product **18** in 85% yield. The formation of *N*-hydroxylactam **15** was rationalized by investigation of the mechanism of reduction. Cyclization of the *N*-hydroxylamine occurred before the *N*-hydroxylamine underwent further reduction.

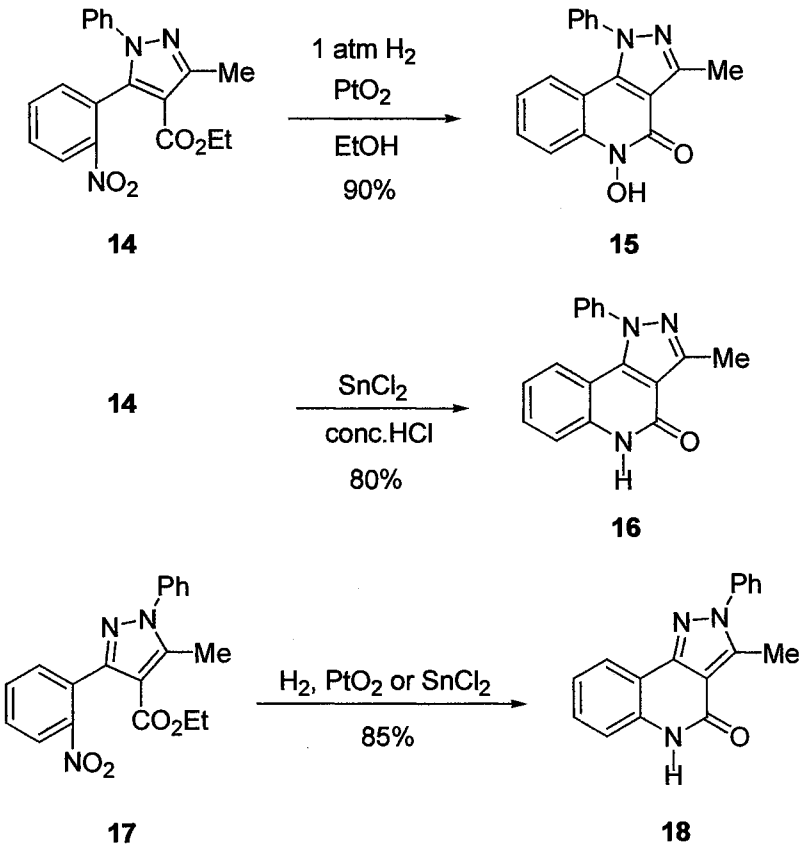
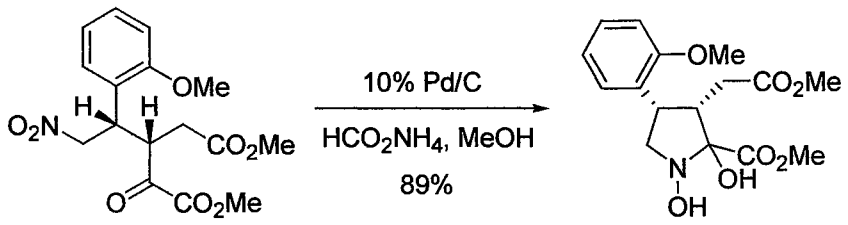


Figure 6. Modification of reduction conditions to produce *N*-hydroxylactams and lactams.

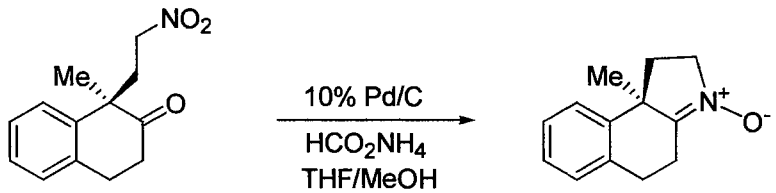
Compounds containing a glutamic acid subunit are of interest for their potential neuroexcitory characteristics. Kraus and co-workers[8] observed the formation of an *N*-hydroxyl product when subjecting nitroketone **19** to reductive cyclization. Reduction of **19** with ammonium formate as the hydrogen transfer agent and a palladium-on-carbon catalyst in methanol produced pyrrolidine **20** in 89% yield (Figure 7).



19 **20**

Figure 7. Reductive cyclization producing an *N*-hydroxylactam.

Similar reduction conditions were employed by Degnan and Meyers[9] in an attempted enantioselective synthesis of 2-aminotetralins (Figure 8). Reduction of nitro ketone **21** using ammonium formate and a palladium-on-carbon catalyst in tetrahydrofuran and methanol produced nitrone **22** in 93% yield. Again, cyclization of the intermediate hydroxylamine with the carbonyl occured before further reduction to the amine.



21 93% **22**

Figure 8. Reductive cyclization producing a nitrone.

Dugat and co-workers[10] also isolated a nitrone product upon reduction of a nitroketone (Figure 9). Treatment of **23** with ammonium formate and a palladium on carbon catalyst produced nitrone **24** in 80% yield. Further reduction of **24** with metallic sodium in ethanol produced amine **25** in 95% yield.

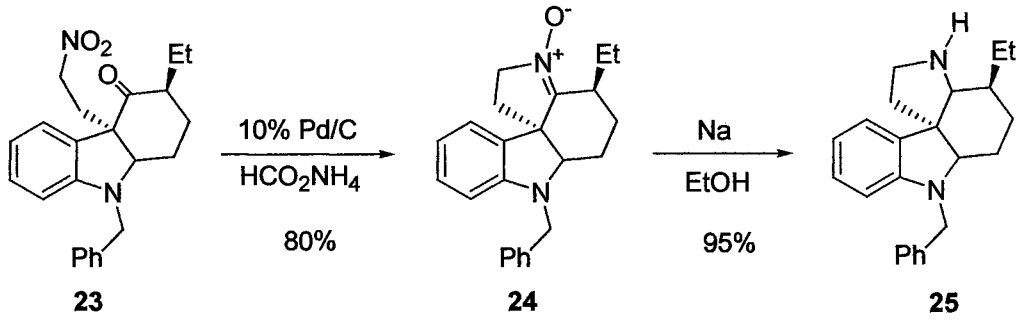


Figure 9. Reductive cyclization producing a nitrone and further reduction to the amine.

Cyclizations with Aldehydes

Artico and co-workers[11] synthesized pyrrolobenzodiazepine derivatives as potential anti-tumor and antibacterial agents. Pyrrolobenzodiazepine derivatives have structures similar to the antibiotic anthramycin. The catalytic hydrogenation of 1-(2-nitrophenyl)-2-pyrrolecarbaldehyde (**26**) in ethyl acetate under 4 atm of hydrogen using 10% palladium-on-carbon in ethyl acetate yielded benzodiazepine **27** (Figure 10).

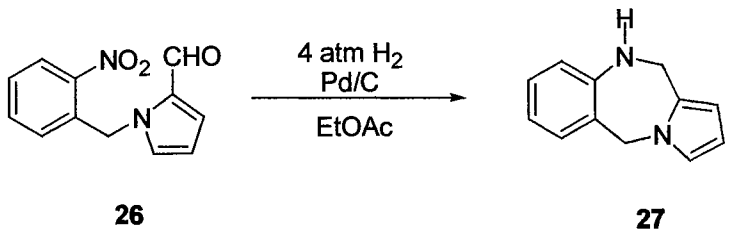
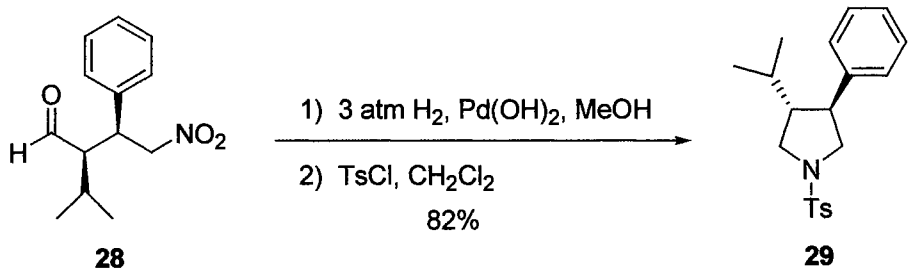


Figure 10. Reductive cyclization of a nitroaldehyde to produce a benzodiazepine derivative.

Substituted, chiral, nonracemic pyrrolidines derived from both natural and unnatural sources are of interest for their potential biological activities and much effort has been devoted to the development of asymmetric syntheses to produce these compounds. Barbas and co-workers[12] utilized the reductive amination of a γ-

nitroaldehyde in the final step of their synthesis of chiral pyrrolidines. For example, γ-nitroaldehyde **28** was catalytically hydrogenated under 3 atm hydrogen with palladium(II) hydroxide in methanol at 20 °C. This was followed by conversion to the *N*-tosyl derivative by treatment with tosyl chloride in methylene chloride to produce pyrrolidine **29** in 82% overall yield (Figure 11).



28 **29**

Figure 11. Reductive cyclization producing a chiral pyrrolidine.

Ventrice and co-workers[13] have investigated the reduction of nitroaromatic compounds bearing aldehyde-containing side chains of various lengths to yield both monomeric and dimeric products (Figure 12). The hydrogenations were carried out at atmospheric pressure with either platinum oxide or 10% palladium-on-carbon catalysts in methanol at 20 °C. Catalytic hydrogenation of **30** yielded 67% of 7-membered ring monomer **31** whereas catalytic hydrogenation of **32** yielded 30% of the macrocyclic dimer **33** and 14% of the monomeric product **34**. Catalytic hydrogenation of **35** yielded 75% of 14-membered ring monomer **36** and 6% of the dimeric product **37**. The formation of dimeric products was rationalized to be the result of a competition between intramolecular versus intermolecular reductive amination.[14] Reactions leading to the formation of smaller rings (7 membered rings) and larger rings (> 14 membered rings) were favored over reactions leading to the formation of medium rings (9-10 membered

rings). These observations are in agreement with thermodynamic data on ring size and bond strain.[15]

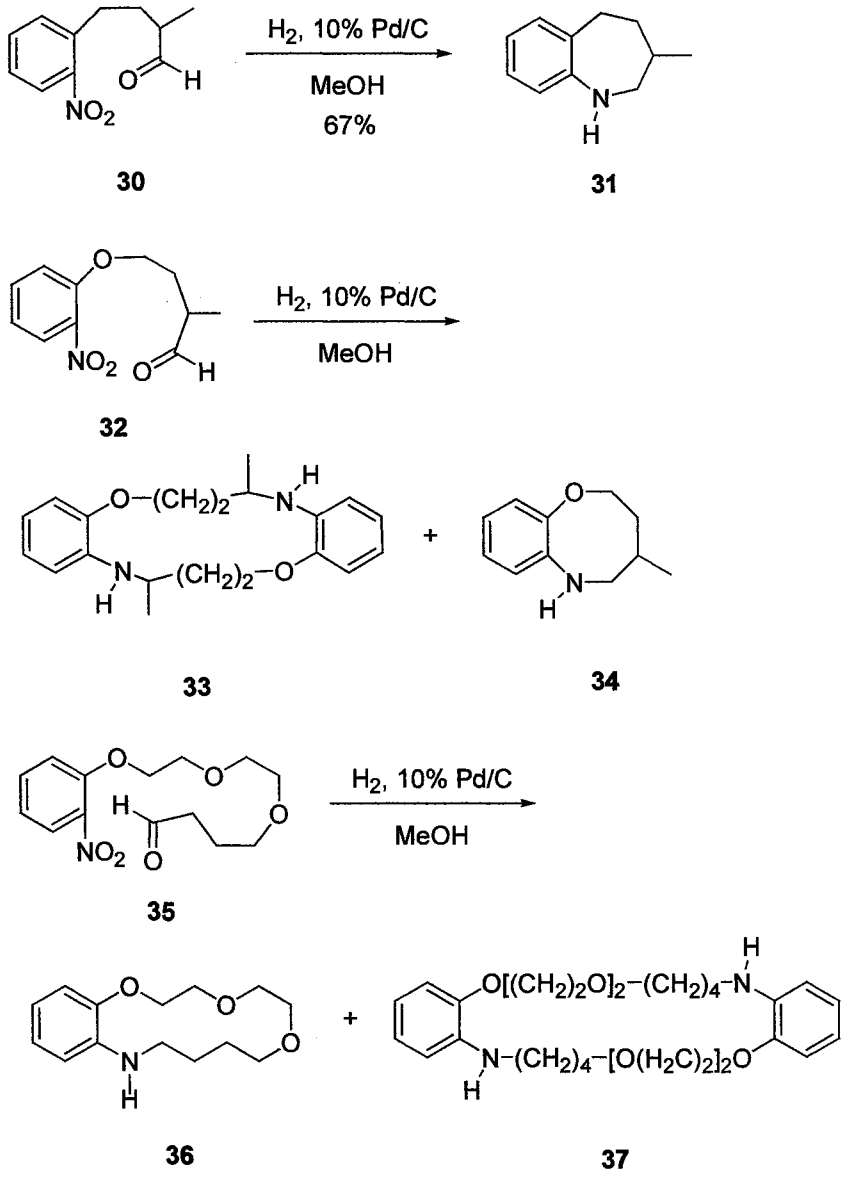
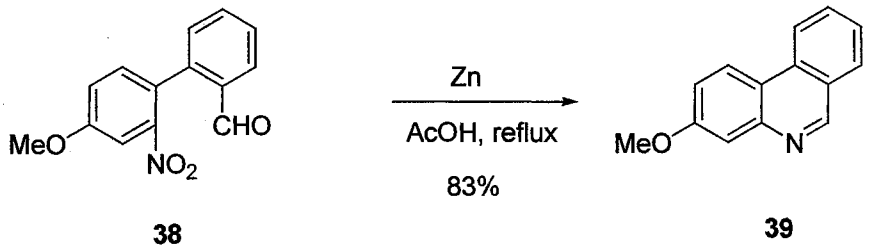


Figure 12. Reductive cyclization of nitroaromatic aldehydes resulting in monomeric and dimeric products.

The addition of one or two equivalents of a chelating agent [$Ag(OTf)_2$, $Ba(NO_3)_2$, or $La(OTf)_{20}$] led to the exclusive formation of monomeric products. This observation

was rationalized by energy minimization calculations in which chelation of the metal to the monomeric product resulted in a lower conformational change than chelation of the metal to the dimeric product.

Zhao and co-workers[16] utilized the reductive cyclization of a nitroaromatic aldehyde in the synthesis of substituted phenanthridines. Substituted phenanthridines are being investigated for use as antitumor agents. In this synthesis, treatment of benzaldehyde derivative **38** with zinc dust in acetic acid at reflux gave phenanthridine product **39** in 83% yield (Figure 13).



38 **39**

Figure 13. Reductive cyclization of nitroaldehyde **38** producing a phenanthridine.

Cyclizations with Ketones

Topliss and co-workers[17] utilized a reductive cyclization reaction in the synthesis of dibenzo[*b*,*f*][*1*,*5*]diazocine derivatives, which were being investigated for their potential sedative and anticonvulsant properties (Figure 14). Catalytic hydrogenation of **40** under 4 atm of hydrogen using a 5% palladium-on-carbon at 20 °C yielded **41**. Reduction of **40** at a higher temperature (40-50 °C) gave **42**. The higher reduction temperature in the second case caused hydrogenolysis of the phenyl ketone before reductive cyclization occurred.

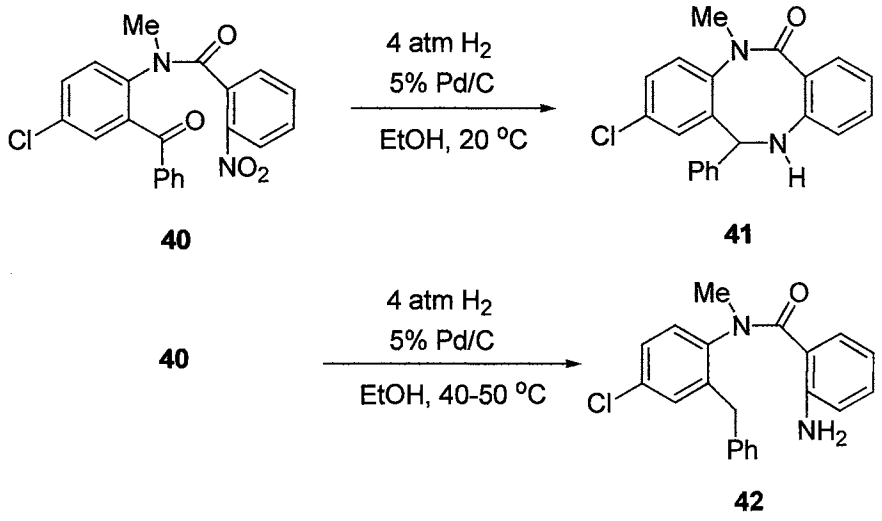
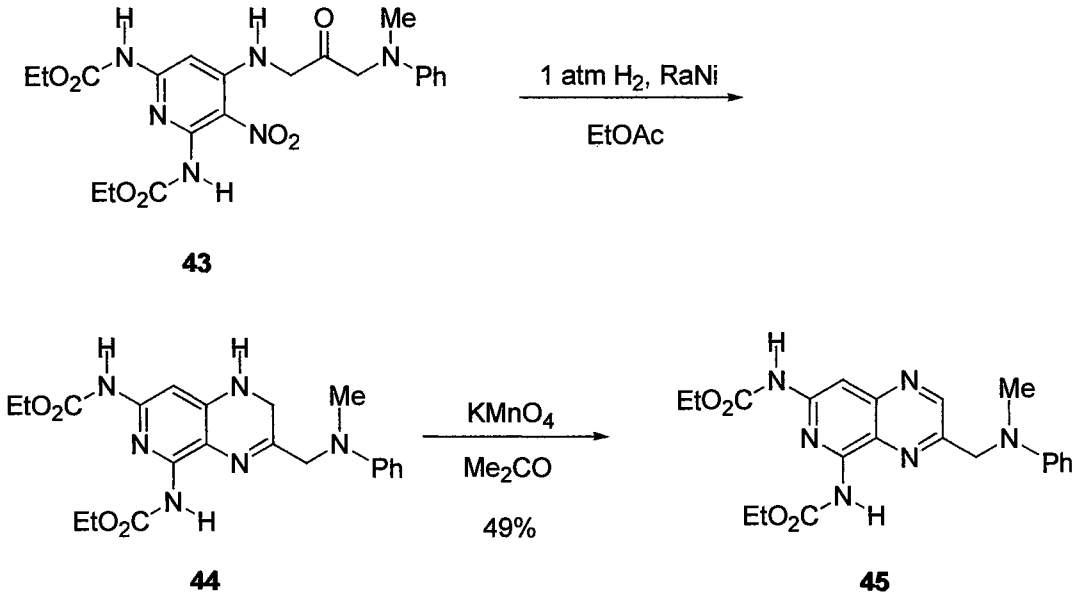


Figure 14. Catalytic hydrogenation of nitrophenylketone **40** under different conditions.

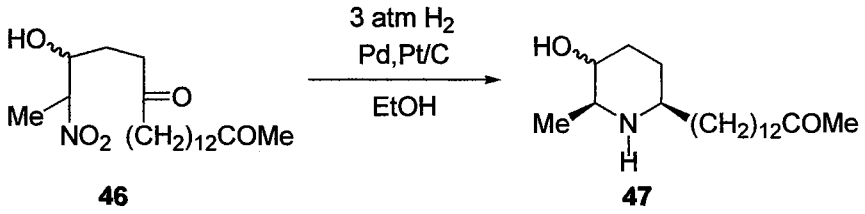
Elliot and co-workers[18] utilized a reductive cyclization in the synthesis of pyrazine derivatives being studied as potential folic acid metabolism inhibitors (Figure 15). Catalytic hydrogenation of **43** under atmospheric pressure using Raney nickel in ethyl acetate at 20 °C yielded **44**. Oxidation of **44** with potassium permanganate in acetone at 20 °C yielded pyrazine **45** in 49% overall yield.



43 **44** **45**

Figure 15. Reductive cyclization and subsequent oxidation of nitroketone **43** producing pyrazine **45**.

Spectaline is an alkaloid found in very small quantities in nature. Paterne and co-workers[19] have reported in their total syntheses of spectaline that catalytic reduction of diastereomeric mixture **46** in ethanol under 3 atm hydrogen with a mixed palladium and platinum-on-carbon catalyst in ethanol at 20 °C produced 2,6-substituted piperidin-3-ol diastereomers **47** (Figure 16). The diastereomers were easily separated by column chromatography with silica gel.



46 **47**

Figure 16. Reductive cyclization of nitroketone **46** producing piperadin-3-ol **47**.

Seeman and co-workers[20] synthesized a series of nicotine derivatives with an additional fused ring hindering the mobility of the parent ring in order to study the pharmacological properties of various nicotine conformations. Reductive cyclization of nitroketone **48** under 3.5 atm hydrogen using a Raney nickel catalyst in ethanol at 20 °C afforded imine **49** in 76% yield. Further reduction of imine **49** with sodium cyanoborohydride in a solution of aqueous hydrochloric acid and methanol produced the desired nornicotine derivative **50** in 53% yield (Figure 17). The stereochemistry of the fused ring was determined by NOE experiments. Irradiation of the bridgehead benzylic proton resulted in an enhancement of the resonance of the other bridgehead proton, demonstrating a cis relationship.

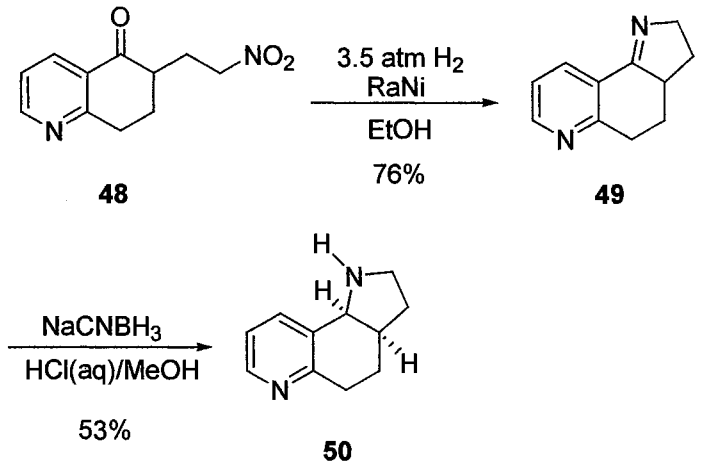


Figure 17. Reductive cyclization and subsequent reduction of nitroketone **48** producing nornicotine derivative (**50**).

CHAPTER II

DIASTEREOSELECTIVE SYNTHESIS OF 2,4-DISUBSTITUTED AND 1,2,4-TRISUBSTITUTED TETRAHYDROQUINOLINES BY A TANDEM REDUCTION-REDUCTIVE AMINATION

Introduction

The tetrahydroquinoline ring system has been of interest for many years due to its presence in many natural products[21] and its biological activity.[22,23] Previous work by Bunce and co-workers[24] demonstrated the use of tandem reduction-Michael addition reactions for the synthesis of tetrahydroquinoline-2-acetic esters. The synthesis involved reduction of an aromatic nitro group followed by intramolecular Michael addition of the resulting amine to an α,β-unsaturated ester to give a benzo-fused nitrogen heterocycle. This work has been extended to reactions of the amine produced from reduction of the aromatic nitro compound with a pendant aldehyde or ketone substituent.

Synthesis of Cyclization Substrates. The first stage of the synthesis is illustrated in Figure 18. Esterification of (2-nitrophenyl)acetic acid (**1**) in methanol saturated with dry HCl gave **2** in 96% yield. Alkylation of **2** with various allylic halides, **3-7**, in dry acetonitrile containing potassium carbonate and a catalytic amount of 18-crown-6 at 55-65 °C produced esters **8-12**. The yields from alkylations using allylic bromides were improved when a catalytic amount of sodium iodide was added to the

reaction mixture. The yields of the alkylations ranged from 46 to 93% and are summarized in Table I.

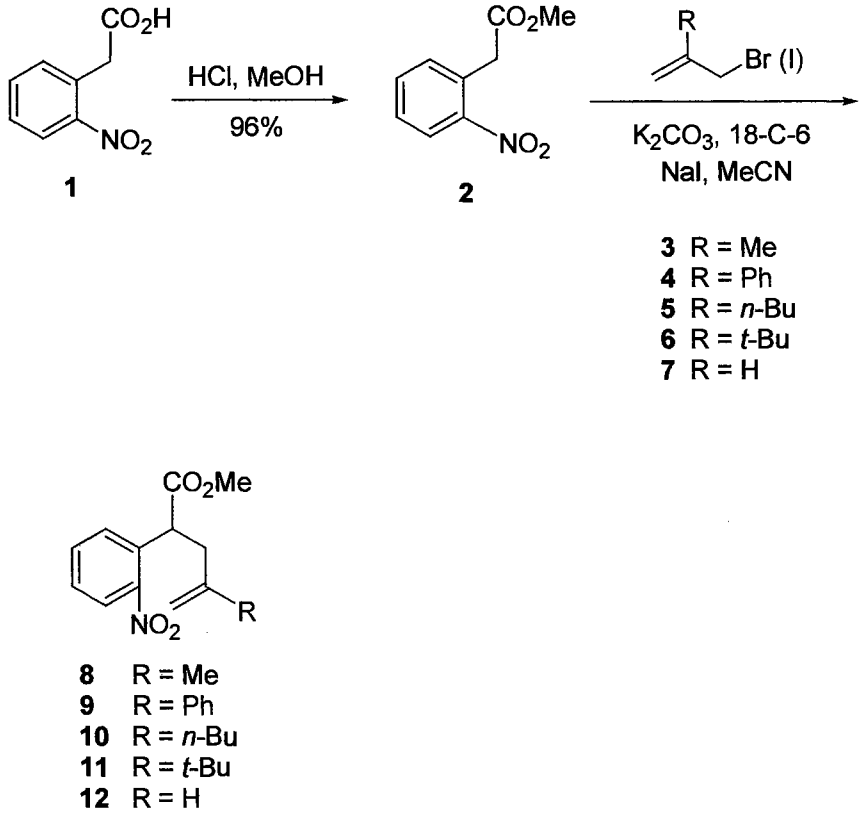


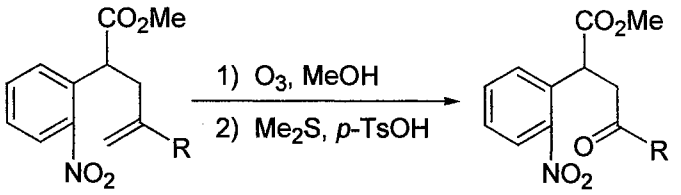
Figure 18. Preparation of methyl 2-nitrophenylacetate (**2**) and subsequent alkylation with substituted allylic halides.

TABLE I

THE ALKYLATION OF METHYL (2-NITROPHENYL)ACETATE WITH 2-SUBSTITUTED ALLYLIC HALIDES

starting allylic halide	R	product	yield (%)
3	Me	**8**	88
4	Ph	**9**	46
5	*n*-Bu	**10**	91
6	*t*-Bu	**11**	93
7	H	**12**	88

Ozonolysis of esters **9-12** in methanol at –78 °C followed by reductive workup with dimethyl sulfide and *p*-toluenesulfonic acid produced ketones **13-16** in yields of 89-95% (Table II) as shown in Figure 19. Ozonolysis of **8** under the same conditions produced the expected aldehyde **17** and approximately 5-10% of the aldehyde dimethyl acetal **18** as shown in Figure 20. Conversion of acetal **18** to aldehyde **17** was accomplished in 98% yield by treatment with a 1:1 mixture of 3% aqueous $HClO_4$ and tetrahydrofuran.



8 R = Me
9 R = Ph
10 R = *n*-Bu
11 R = *t*-Bu

13 R = Me
14 R = Ph
15 R = *n*-Bu
16 R = *t*-Bu

Figure 19. Ozonolysis of methyl (±)-4-alkyl-2-(2-nitrophenyl)-4-pentenoates.

TABLE II

OZONOLYSIS OF 4-ALKYL-2-(2-NITROPHENYL)-4-PENTENOIC ESTERS

starting alkene	R	product	yield (%)
8	Me	**13**	94
9	Ph	**14**	89
10	*n*-Bu	**15**	95
11	*t*-Bu	**16**	92

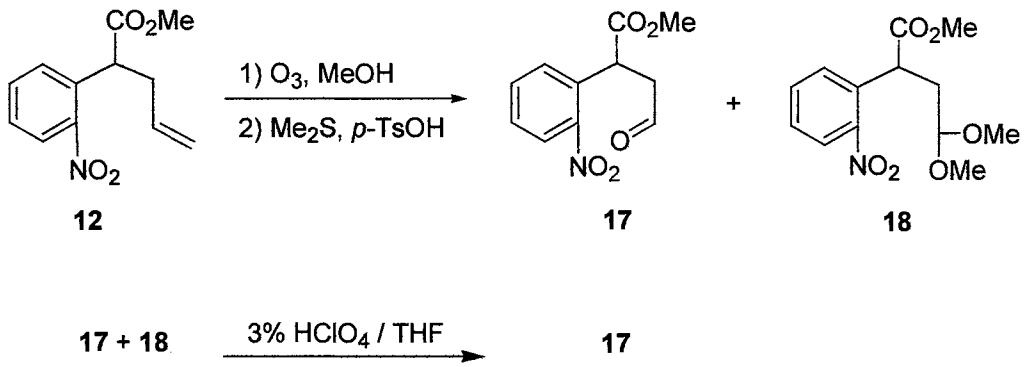
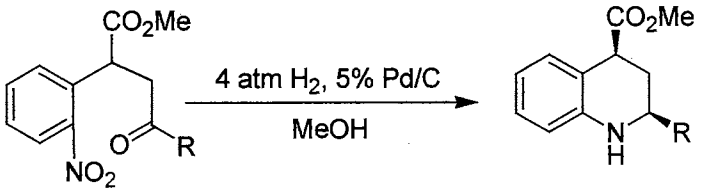


Figure 20. Ozonolysis of alkene **12** followed by complete conversion to the aldehyde.

The reduction-reductive amination of compounds **13-17** is illustrated in Figure 21. Hydrogenation in methanol using a 5% palladium-on-carbon catalyst produced the 1,2,3,4-tetrahydroquinoline products **19-23** in yields from 88-99% (Table III). The 2,4-disubstituted 1,2,3,4-tetrahydroquinoline products **19-22** were isolated as single diastereomers with a cis relationship between the substituents at C2 and C4.



13 R = Me
14 R = Ph
15 R = *n*-Bu
16 R = *t*-Bu
17 R = H

19 R = Me
20 R = Ph
21 R = *n*-Bu
22 R = *t*-Bu
23 R = H

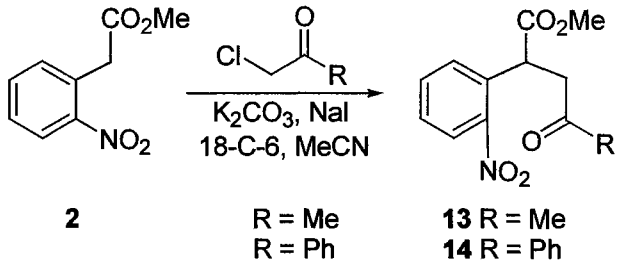
Figure 21. Tandem reduction-reductive amination of nitro ketones.

TABLE III

TANDEM REDUCTION-REDUCTIVE AMINATION OF NITROKETONES

starting ketone	R	product	yield (%)
13	Me	**19**	98
14	Ph	**20**	97
15	*n*-Bu	**21**	99
16	*t*-Bu	**22**	93
17	H	**23**	88

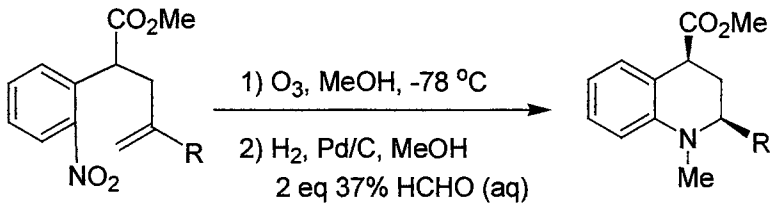
A variation of the procedure was attempted by alkylating **2** with α-chloroketones (Figure 22). This was intended to provide a more direct means of synthesizing nitroketones **13-16**. Alkylation of **2** with chloroacetone by the method described above yielded ketone **13** in 56% yield. Attempted alkylation of **2** with phenacyl chloride, however, gave none of the phenyl ketone product. The lower yield and limited scope of this reaction led us to abandon this approach.



2 R = Me, R = Ph **13** R = Me **14** R = Ph

Figure 22. Attempted alkylation of methyl 2-nitrophenylacetate with α-chloroketones.

Syntheses of 1,2,4-Trisubstituted-1,2,3,4-Tetrahydroquinolines. Synthesis of 1,2,4-trisubstituted-1,2,3,4-tetrahydroquinolines **24-27** was accomplished by modifying the procedure (Figure 23). The alkylation products **13-16** were ozonized in methanol, but the treatment with dimethyl sulfide and *p*-toluenesulfonic acid was omitted. Instead, two equivalents of 37% aqueous formaldehyde were added to the crude ozonolysate and hydrogenation was carried out directly. This afforded the 1-methyl derivatives of the 2,4-trisubstituted tetrahydroquinoline products **24-27** in yields of 73-80% (Table IV). Presumably, different alkyl groups could be added by using different aldehydes. The 1,2,4-trisubstituted products **24-27** were isolated as single diastereomers with the substituents on C2 and C4 demonstrating a cis relationship.



9 R = Me
10 R = Ph
11 R = *n*-Bu
12 R = *t*-Bu

24 R = Me
25 R = Ph
26 R = *n*-Bu
27 R = *t*-Bu

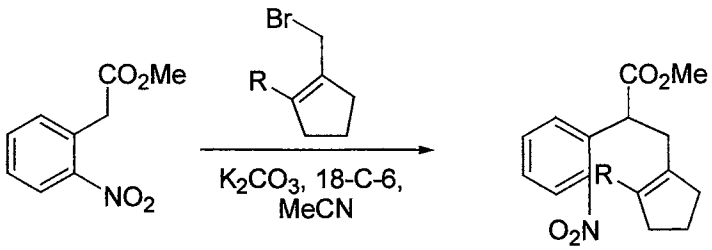
Figure 23. Ozonolysis and tandem reduction-reductive amination sequence leading to 1,2,4 trisubstituted products.

TABLE IV

OZONOLYSIS FOLLOWED BY TANDEM REDUCTION-REDUCTIVE AMINATION OF NITROKETONES

starting ketone	R	product	yield (%)
13	Me	**24**	80
14	Ph	**25**	73
15	*n*-Bu	**26**	76
16	*t*-Bu	**27**	74

Synthesis of Tricyclic 1,2,3,4-Tetrahydroquinoline Derivatives. Alkylation of **2** with 1-(bromomethyl)cyclopentene (**28**) or 1-(bromomethyl)-2-methylcyclopentene (**29**) by the method described previously produced alkylated nitro esters **30** and **31** in yields of 76 and 82%, respectively (Figure 24).



2 **28** R = H, **29** R = Me → **30** R = H, **31** R = Me

Figure 24. Alkylation of methyl 2-nitrophenylacetate with 1-(bromomethyl) cyclopentenes.

The synthesis of tricyclic product **34** is shown in Figure 25. Ozonolysis and reductive workup of ester **30** produced a mixture of ketoaldehyde **32** and keto acetal **33**. Treatment of the mixture of **32** and **33** with 3% aqueous $HClO_4$ in tetrahydrofuran as described for **17** and **18** produced the ketoaldehyde **32** in 94% yield. Hydrogenation of **32** then produced the tricyclic product **34** in 69% yield. The fused ring residue at C2 and the ester group on C4 again displayed a cis relationship.

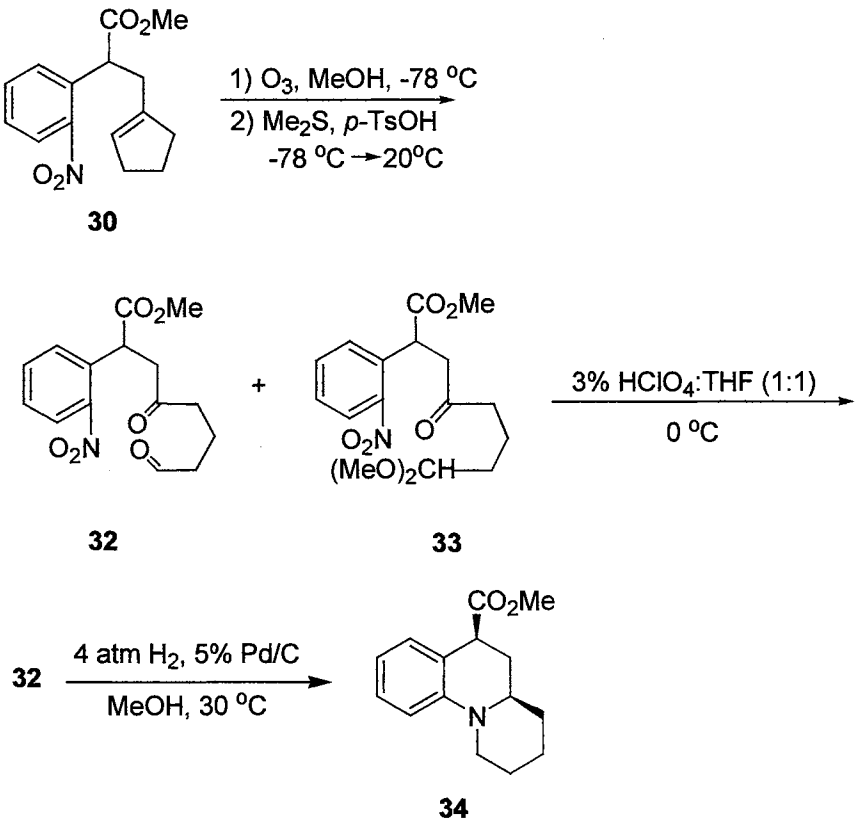


Figure 25. Tandem reduction-reductive amination to form a tricylic compound.

Ozonolysis and reductive workup of ester **31** produced diketone **35** in 95% yield (Figure 26). Hydrogenation of diketone **35** by the standard conditions gave a mixture of products, with the major band being the expected tricyclic product **36** in 60% yield. Analysis of the other bands revealed two side products, **37** and **38**, in yields of 6% and 2%, respectively.

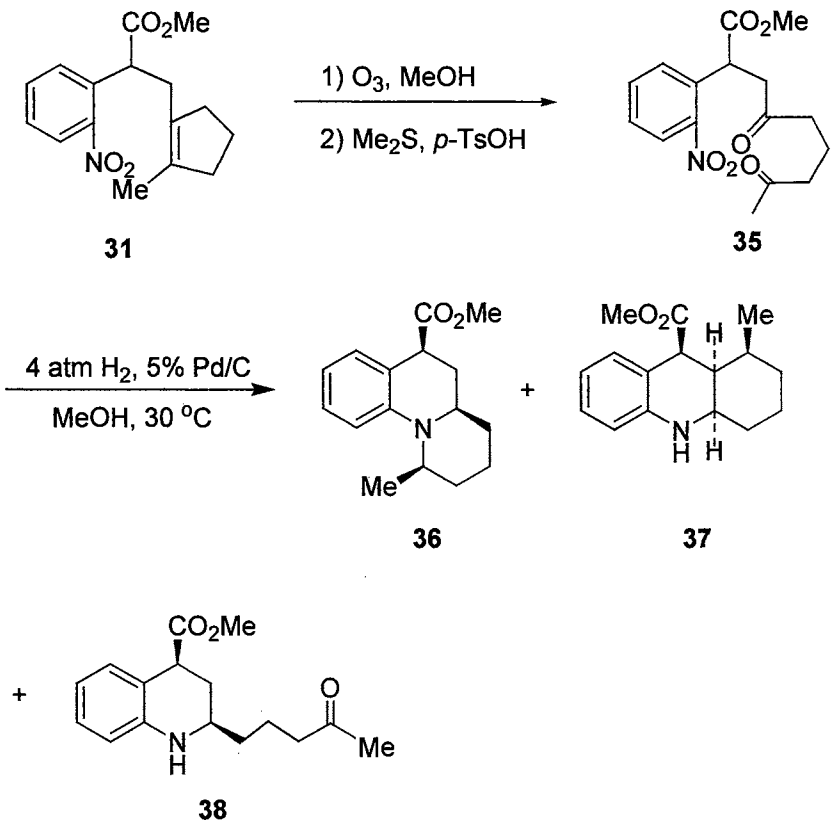


Figure 26. Ozonolysis of 2-methyl-1-cyclopentenyl substituted ester followed by tandem reduction-reductive amination.

Diastereoselectivity in the Reduction-Reductive Amination. The cis selectivity demonstrated in the formation of the 2,4-disubstituted (**19-22**) and 1,2,4-trisubstituted 1,2,3,4-tetrahydroquinoline (**24-27**) products can be rationalized by investigation of the mechanism of the reduction (Figure 27). The exact chronology of steps is unknown, but the reaction sequence likely begins with reduction of the aromatic nitro group to an amine (**39**) or *N*-hydroxylamine. Condensation with the carbonyl group followed by dehydration produces imine **40**. The double bond of **40** possesses two diastereotopic faces, one of which is partially blocked by the ester group. Addition of hydrogen in the final reduction occurs at the opposite face, producing products **19-22** with the C2 substituent cis to the C4 ester group. Formation of the *N*-methyl products

24-27 occurs by a similar mechanism with an additional reductive amination between the formaldehyde and the tetrahydroquinoline nitrogen.

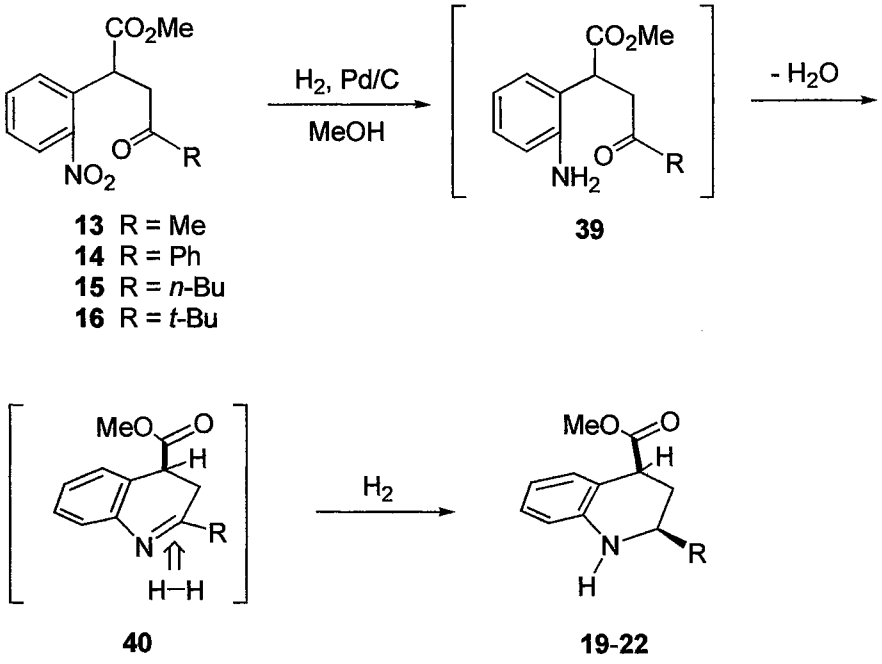


Figure 27. Proposed mechanism of the tandem reduction-reductive amination.

The cis relationship between the C2 ring residue and the C4 ester group in product **36** results from reduction of imine **41**, producing intermediate **42**. Condensation of the tetrahydroquinoline nitrogen with the side chain carbonyl group results in closure of the ring to produce enamine **43**. The final addition of hydrogen to intermediate **43** occurs to the molecular face opposite the C4 ester, resulting in a cis relationship between the methyl group, the ring residue, and the ester group. Product **37** is formed by tautomerization of imine **41** to enamine **44**, which subsequently adds to the side chain ketone (Figure 28). Finally, product **38** is formed by reduction of the nitro group followed by a single reductive ring closure (Figure 29).

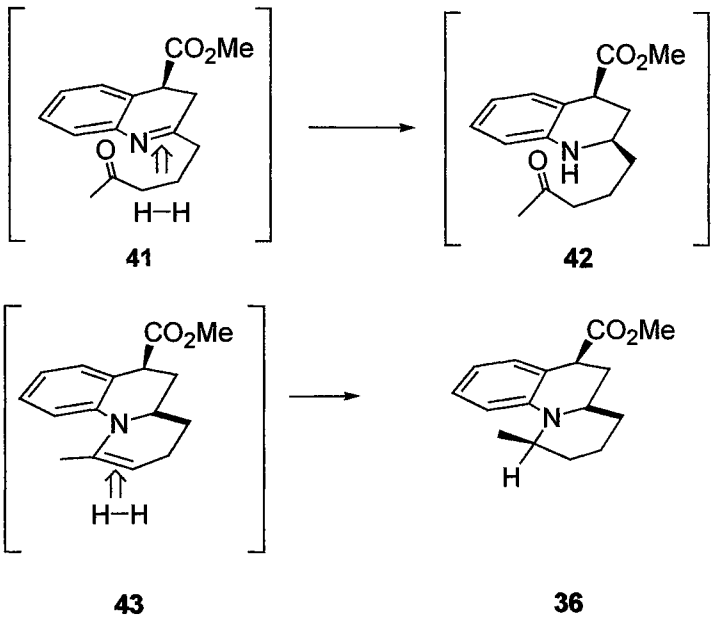


Figure 28. Intermediates leading to the formation of product **36**.

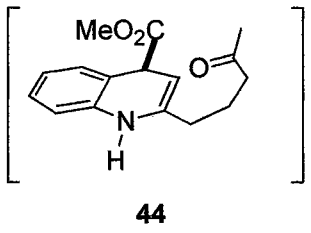


Figure 29. Intermediate leading to the formation of product **37**.

Spectroscopic Determination of Stereochemistry. The ^{1}H NMR and X-ray crystallographic data compiled by Crabb and co-workers[25] show that the heterocyclic ring of 1,2,3,4-tetrahydroquinolines adopts a half chair conformation. The cis relationship between the C2 alkyl and C4 carboxylate ester in products **19-22** was determined by the magnitude of coupling constants in the ^{1}H NMR spectra and application of the Karplus relationship. The cis assignment can be demonstrated using the C2 methyl product **19** as an example (Figure 30). The signal assignments were confirmed by a COSY-45

spectrum (Plate I). In the ^{1}H NMR spectrum, the most downfield signal in the aliphatic region (δ 3.96) is assigned to H4 which is coupled to the two protons on C3 ($J_{4,3ax}$ = 12.0 Hz, $J_{4,3eq}$ = 5.9 Hz). The magnitude of these coupling constants indicates a dihedral angle of nearly 180° between the coupled protons; thus the ester group on C4 is in a pseudoequatorial position and the proton is in a pseudoaxial position. The signal at δ 3.41 is assigned to H2 which is coupled to the two protons on C3 ($J_{2,3ax}$ = 11.5 Hz, $J_{4,3eq}$ = 2.6 Hz) and the methyl substituent ($J_{2,Me}$ = 6.3 Hz). The large coupling constant between H2 and $H3_{ax}$ also indicates a dihedral angle of nearly 180° between these protons indicating that the C2 methyl is in a pseudoequatorial position and the proton is in a pseudoaxial position. Pseudo-equatorial placement of the substituents on C2 and C4 indicates that the groups are cis.

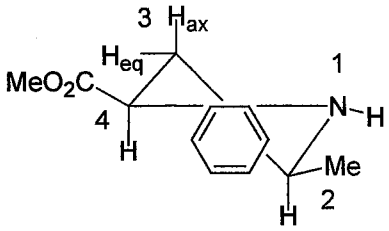


Figure 30. Half chair conformation of methyl product (**19**).

The relative stereochemistry of the two substituents on the heterocyclic ring was further confirmed by a NOESY spectrum (Plate II) of C2 methyl product **19**. An NOE crosspeak is observed between H4 at δ 3.96 and H2 at δ 3.41. The presence of the crosspeak demonstrates the near 1,3-diaxial relationship between these two protons and thus the cis relationship between the two ring substituents.

The cis relationship between the ester group, the ring methylene, and the methyl substituent of tricyclic product **36** was also confirmed by a NOESY spectrum (Plate III).

A correlation is observed between H_a and H_c with H_b, placing these protons in a 1,3-diaxial like relationship with each other (Figure 31). The structure of product **37** was also confirmed by a NOESY spectrum.

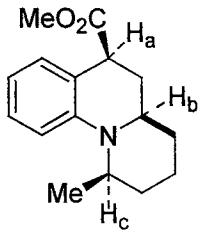


Figure 31. Illustration of the cis relationship between the ester group, the ring methylene, and the methyl substituent in product **36**.

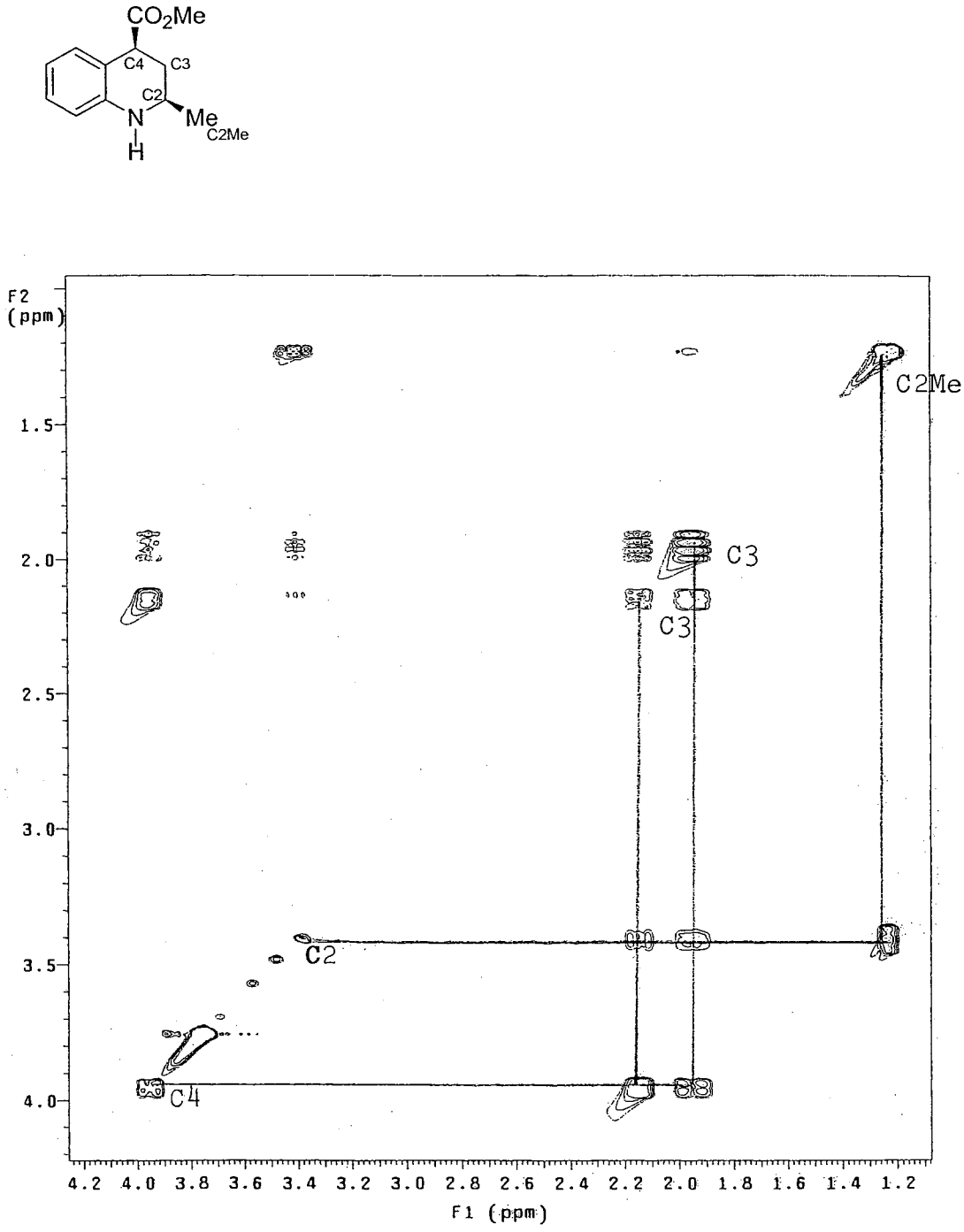
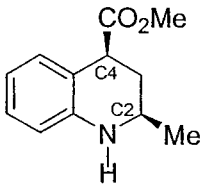


Plate I. COSY of Methyl (±)-(2*R**,4*S**)-2-Methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (**19**).



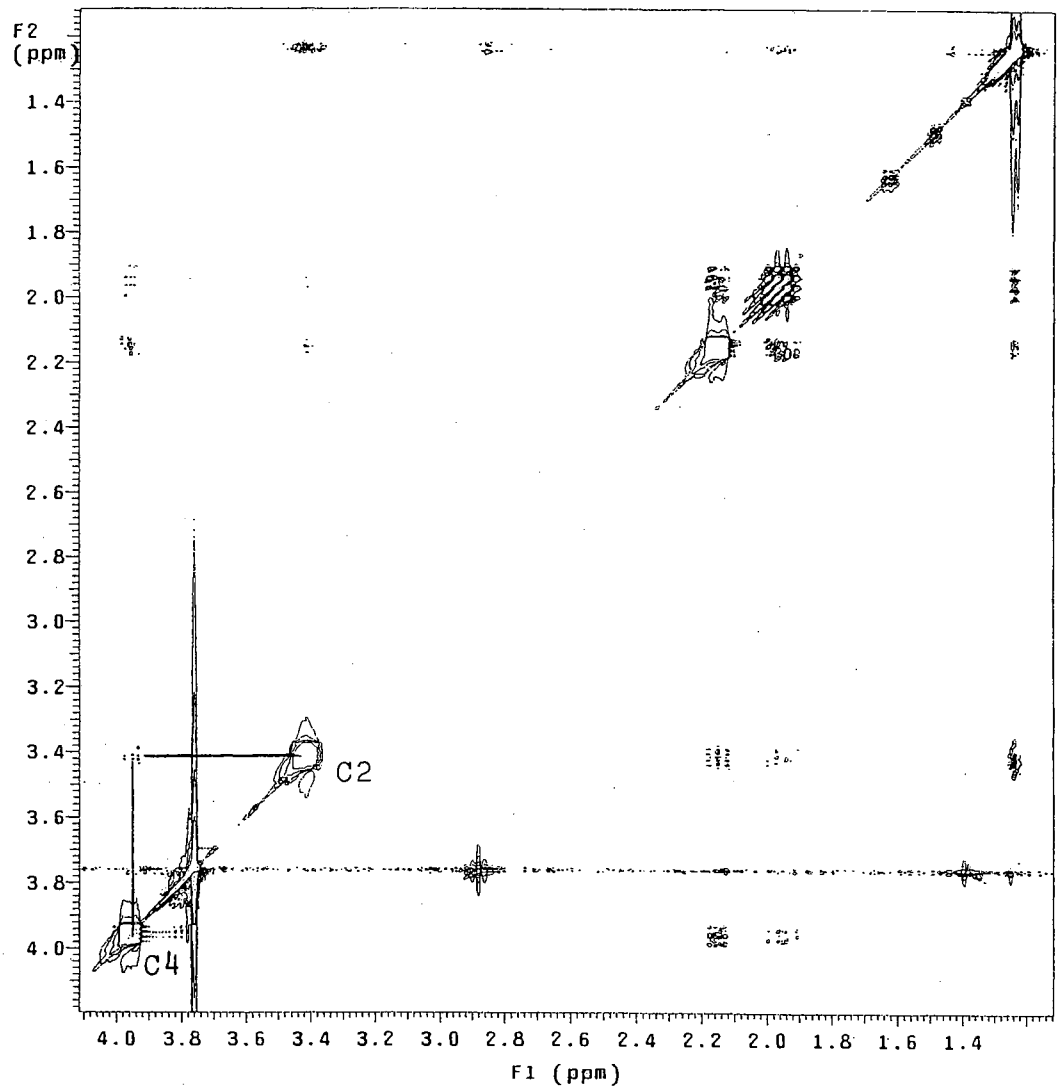
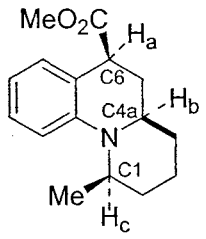


Plate II. NOESY of Methyl (±)-(2*R**,4*S**)-2-Methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (**19**).



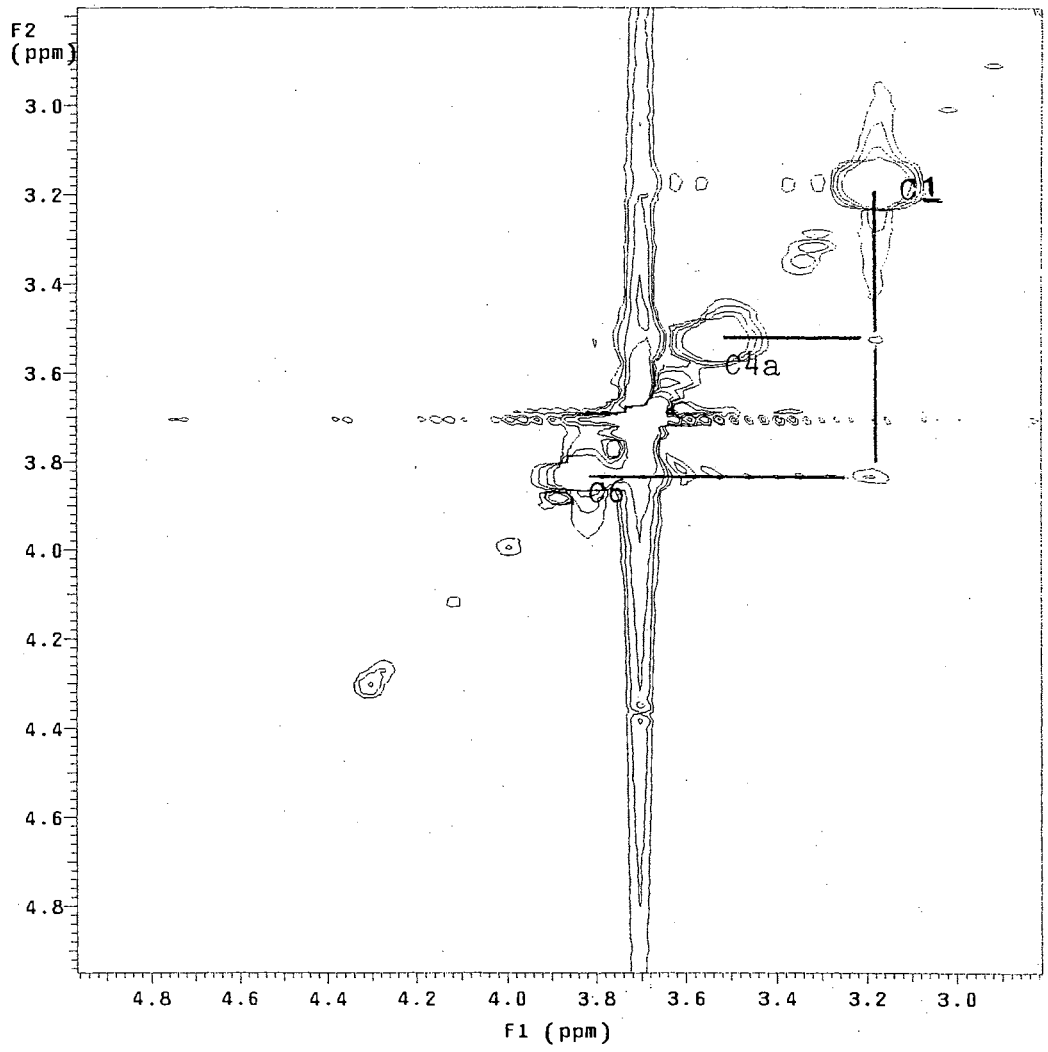


Plate III. NOESY of Methyl (±)-(1*R**,4a*R**,6*S**)-1-Methyl-2,3,4,4a,5,6- hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate (**36**).

Discussion. The key step in the synthesis is the tandem reduction-reductive amination sequence initiated by catalytic reduction of the nitro group. In substrates incorporating a ketone group, reduction of the final imine intermediate **41** was highly diastereoselective, resulting from addition of hydrogen to the face opposite the ester group. This resulted in the formation of a single product having a cis relationship between the C2 alkyl and the C4 ester groups in products **19-22**. This synthesis was extended to include the synthesis of 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters **24-27** in which the C2 alkyl and C4 ester groups also displayed a cis relationship. The synthesis of methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (**23**) was also accomplished by the same tandem reduction-reductive amination procedure.

The synthesis of fused tricyclic products **34** and **36** by reduction-double reductive amination has been accomplished. The synthesis of fused tricyclic product **34** was also diastereoselective, resulting in formation of a product having a cis relationship between the C4 ester group and the C2 fused ring residue. In the synthesis of **36**, the major product displayed a cis relationship between the C4 ester group, the C2 alkyl group, and the methyl substituent.

Conclusion. This work represents a new synthetic approach to the production of 2-alkyl and 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters, as well as related tricyclic structures. The C4 ester group acts as a stereodirecting group in the reductive cyclization for the addition of hydrogen to the final imine, resulting in the formation of the product as a single diastereomer. This methodology in which the ester group directs the addition of hydrogen to a double bond can be applied to the construction of more complex ring systems.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Potassium carbonate was ground into a fine powder, dried under vacuum for 24 h at 120 °C, and then stored in an oven at 120 °C until needed. Allylic halides **3** and **4** were commercially available. The allylic halides needed for the syntheses of compounds **10-12** were prepared by the following methods: 3-iodo-2-phenylpropene (**5**) was prepared by the method of Bunce and Zimmerman;[26] 3-bromo-2-butylpropene (**6**) was prepared by (1) addition of HBr to 1-hexyne,[27] (2) conversion to the Grignard reagent followed by reaction with formaldehyde gas and (3) conversion of the alcohol to the bromide by reaction with PBr_3 (38% overall yield); 3-bromo-2-*tert*-butylpropene (**7**) was prepared following the procedure of Dauben and co-workers;[28] 1-(bromomethyl)-1-cyclopentene (**28**) was prepared by (1) reduction of cyclopentene-1-carboaldehyde[29] with lithium aluminum hydride and (2) conversion of the alcohol to the bromide by treatment with PBr_3;[30] 1-(bromomethyl)-2-methyl-1-cyclopentene (**29**) was prepared from 2-methyl-1-cyclopentene-1-carboxaldehyde[31] according to the procedure of Ziegler and co-workers.[32]

All reactions were run under dry nitrogen and in oven-dried glassware. The HCl (0.2 M, 1 M, 2 M, and 6 M), NaOH (0.2 M and 1 M), $NaHCO_3$ (saturated), $Na_2S_2O_3$ (5%), and NaCl (saturated) used in various procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on silica gel GF plates (Analtech no. 21521) with UV detection, or (2) capillary GC (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50-300 °C. Preparative separations were performed by one of the following methods: (1) flash column chromatography on silica gel (grade 62, 60-200 mesh) containing UV-active

phosphor (Sorbent Technologies UV- 5) or (2) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Band elution for both methods was monitored by using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and referenced to polystyrene. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz respectively using $(CH_3)_4Si$ as an internal standard. COSY and NOESY spectra were recorded at 400 MHz. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Esterification of 2-Nitrophenylacetic Acid (1): Methyl (2-Nitrophenyl) Acetate (2). A saturated solution of HCl in 500 mL of anhydrous methanol[33] was prepared in a 1000-mL, three-necked, round-bottomed flask fitted with a reflux condenser and a magnetic stir bar. To this solution was added 50.0 g (276 mmol) of **1**. The solution was refluxed for approximately 15 h. After cooling to room temperature, the solution was concentrated under vacuum, diluted with saturated NaCl, and extracted with 100 mL of ether (3x). The combined organic layers were washed with $NaHCO_3$ (2x), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude ester as a yellow oil. Vacuum distillation then gave 51.7 g (265 mmol, 96%) of a pale yellow oil, bp 115-117 °C (0.1 mm Hg). IR 1735, 1521, 1348 cm^{-1}; ^{1}H NMR δ 8.12 (d, J = 8.1 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 1 H), 7.36 (d, J = 7.5 Hz, 1 H), 4.04 (s, 2 H), 3.72 (s, 3 H); ^{13}C NMR δ 170.4, 148.7, 133.6, 133.3, 129.7, 128.6, 125.3, 52.2, 39.5.

Representative Procedure for the Alkylation of Methyl (2-Nitrophenyl)acetate (2): Methyl (±)-2-(2-Nitrophenyl)-4-pentenoate (8). The general procedure of Makosza and Tyrala[34] was used. A 250-mL, three-necked, round-bottomed

flask containing a magnetic stir bar was charged with 100 mL of dry acetonitrile, 15 mg of 18-crown-6, and 17.4 g (126 mmol) of anhydrous potassium carbonate. Stirring was started and 2.93 g (15.0 mmol) of **2** was added. To the resulting blue solution was added, 2.72 g (18.8 mmol) of **3** and the solution was stirred at 55-65 °C. The progress of the reaction was monitored by TLC. After 9 h, TLC indicated that the reaction was not complete and 0.25 g (1.67 mmol) of sodium iodide was added. The reaction was stirred for a total of 18 h and then allowed to cool to room temperature. The reaction mixture was vacuum filtered to remove potassium carbonate and other insoluble salts, dissolved into ether, washed with $Na_2S_2O_3$ (3x) and NaCl (2x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-15%) to yield 3.09 g (12.2 mmol, 88%) of **9** as a light yellow oil. IR 1736, 1641, 1532, 1350 cm^{-1}; ^1H NMR δ 7.90 (dd, J = 8.2, 1.4 Hz, 1 H), 7.62-7.51 (complex, 2 H), 7.43 (m, 1 H), 5.73 (ddt, J = 17.1, 10.1, 6.9 Hz, 1 H), 5.05 (dm, J = 17.1 Hz, 1 H), 5.01 (dm, J = 10.1 Hz, 1 H), 4.31 (t, J = 7.5 Hz, 1 H), 3.68 (s, 3 H), 2.91 (m, 1 H), 2.63 (m, 1 H); ^{13}C NMR δ 172.7, 149.5, 134.5, 133.1, 133.0, 130.2, 128.2, 124.8, 117.9, 52.2, 46.0, 36.8; HRMS *m/z*: Calcd for $C_{12}H_{13}NO_4$: 235.0844; Found 235.0847.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.28; H, 5.53. Found: C, 61.54; H, 5.58.

Methyl (±)-4-Methyl-2-(2-nitrophenyl)-4-pentenoate (9). 3.30 g (13.3 mmol, 88%); IR 1737, 1659, 1523, 1353 cm^{-1}; ^1H NMR δ 7.88 (d, J = 8.2 Hz, 1 H), 7.58 (m, 2 H), 7.42 (m, 1 H), 4.75 (s, 1 H), 4.48 (t, J = 7.5 Hz, 1 H), 3.67 (s, 3 H), 2.87 (dd, J = 14.4, 7.5 Hz, 1 H), 2.55 (dd, J = 14.4, 7.5 Hz, 1 H) 1.73 (s, 3 H); ^{13}C NMR δ 172.8,

149.5, 141.8, 133.0, 130.0, 128.1, 124.7, 113.2, 52.3, 44.4, 40.8, 22.2; HRMS *m/z* Calcd for $C_{13}H_{15}NO_4$: 249.1001; Found: 249.0998.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02. Found: C, 62.78; H, 6.05.

Methyl (±)-4-Phenyl-2-(2-nitrophenyl)-4-pentenoate (10). 0.50 g (1.61 mmol, 46%); IR 1736, 1635, 1530, 1353 cm^{-1}; ^1H NMR δ 7.88 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.41-7.24 (complex, 7 H), 5.19 (s, 1 H), 4.94 (s, 1 H), 4.29 (dd, J = 8.3, 6.6 Hz, 1 H), 3.63 (s, 3 H), 3.53 (dd, J = 13.7, 6.6 Hz, 1 H), 3.03 (dd, J = 13.7, 8.3 Hz, 1 H); ^{13}C NMR δ 172.5, 149.6, 145.1, 139.9 (2), 131.1, 128.4, 128.2, 127.8, 126.2, 124.8, 115.4, 52.2, 46.0, 38.2; HRMS *m/z*: Calcd for $C_{18}H_{17}NO_4$: 311.1157; Found: 311.1154.

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.47. Found: C, 69.66; H, 5.48.

Methyl (±)-4-Butyl-2-(2-nitrophenyl)-4-pentenoate (11). 2.65 g (9.10 mmol, 91%); IR 1744, 1646, 1532, 1354 cm^{-1}; ^1H NMR δ 7.87 (d, J = 7.8 Hz, 1 H), 7.57 (m, 2 H), 7.41 (m, 1 H), 4.75 (s, 1 H), 4.66 (s, 1 H), 4.47 (dd, J = 8.0, 7.1 Hz, 1 H), 3.67 (s, 3 H), 2.87 (dd, J = 14.7, 8.0 Hz, 1 H), 2.54 (dd, J = 14.7, 7.1 Hz, 1 H), 2.00 (t, J = 7.3 Hz, 2 H), 1.42 (complex, 4 H), 0.89 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.9, 149.4, 145.9, 133.1, 132.9, 129.9, 128.1, 124.7, 111.7, 52.3, 44.5, 39.1, 35.5, 29.8, 22.3, 13.9; HRMS *m/z*: Calcd for $C_{16}H_{21}NO_4$: 291.1470; Found: 291.1470.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.22. Found: C, 66.09; H, 7.25.

Methyl (±)-4-*tert*-Butyl-2-(2-nitrophenyl)-4-pentenoate (12). 3.52 g (12.1 mmol, 93%); IR 1745, 1645, 1530, 1353 cm^{-1}; ^1H NMR δ 7.87 (d, J = 7.8 Hz, 1 H), 7.58 (m, 2 H), 7.42 (m, 1 H), 4.89 (s, 1 H), 4.57 (s, 1 H), 4.56 (m, 1 H), 3.67 (s, 3 H), 2.93 (dd, J = 16.4, 8.0 Hz, 1 H), 2.56 (dd, J = 16.4, 7.4 Hz, 1 H), 1.04 (s, 9 H); ^{13}C NMR

δ 173.0, 153.9, 149.5, 133.4, 132.9, 129.8, 128.1, 124.7, 107.7, 50.3, 44.7, 36.2, 34.3, 29.0; HRMS *m/z*: Calcd for $C_{16}H_{21}NO_4$: 291.1470; Found: 291.1469.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.22. Found: C, 66.17; H, 7.23.

Representative Procedure for Ozonolysis: Methyl (±)-2-(2-Nitrophenyl)-4-oxopentanoate (13). A solution containing 1.25 g (5.02 mmol) of **8** in 125 mL of methanol was cooled to –78 °C and treated with ozone until TLC indicated that all of the starting material had been consumed. The reaction was quenched at –78 °C by the addition of 5.08 g (6.00 mL, 84.9 mmol) of dimethyl sulfide and 200 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred, allowed to warm to room temperature over 8 h, and concentrated under reduced pressure. The resulting yellow oil was flash chromatographed on a 30 cm x 2 cm silica gel column eluted with increasing concentrations of ether in hexanes (5–15%) to yield 1.18 g (4.72 mmol, 94%) of **13** as a light yellow oil. IR 1742, 1715, 1528, 1353 cm^{-1}; ^1H NMR δ 7.97 (d, J = 8.0 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.44 (m, 2 H), 4.69 (dd, J = 8.2, 4.8 Hz, 1 H), 3.66 (s, 1 H), 3.48 (dd, J = 18.1, 8.2 Hz, 1 H), 2.87 (dd, J = 18.1, 4.8 Hz, 1 H), 2.20 (s, 3 H); ^{13}C NMR δ 205.2, 172.2, 149.4, 133.5 (2), 131.0, 128.5, 125.2, 52.5, 46.3, 42.7, 29.8; HRMS *m/z*: Calcd for $C_{12}H_{13}NO_5$: 251.0793; Found: 251.0791.

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.69; H, 5.23.

Methyl (±)-2-(2-Nitrophenyl)-4-oxo-4-phenylbutanoate (14). mp 80-82 °C; 1.41 g (4.50 mmol, 89%); IR 1746, 1687, 1530, 1353 cm^{-1}; ^1H NMR δ 7.98 (m, 3 H), 7.57 (m, 3 H), 7.46 (m, 3 H), 4.91 (dd, J = 7.8, 5.1 Hz, 1 H), 4.03 (dd, J = 18.1, 7.8 Hz, 1 H) 3.69 (s, 1 H), 3.47 (dd, J = 18.1, 5.1 Hz, 1 H); ^{13}C NMR δ 196.7, 172.4, 149.3,

136.2, 133.5, 133.4, 131.0, 128.5, 128.1, 125.2, 52.6, 42.8, 42.0; HRMS *m/z*: Calcd for $C_{17}H_{15}NO_5$: 313.0950; Found: 313.0948.

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.18; H, 4.79. Found: C, 65.50; H, 4.84.

Methyl (±)-2-(2-Nitrophenyl)-4-oxooctanoate (15). 1.04 g (3.55 mmol, 95%); IR 1744, 1715, 1527, 1354 cm^{-1}; ^1H NMR δ 7.97 (d, J = 8.1 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 1 H), 4.70 (dd, J = 8.4, 4.8 Hz, 1 H), 3.66 (s, 1 H), 3.44 (dd, J = 18.1, 8.4 Hz, 1 H), 2.85 (dd, J = 18.1, 4.8 Hz, 1 H), 2.45 (m, 2 H), 1.57 (quintet, J = 7.3 Hz, 2 H), 1.30 (sextet, J = 7.4 Hz, 2 H) 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 207.8, 172.3, 148.7, 133.5 (2), 131.0, 128.4, 125.2, 52.5, 45.4, 42.7, 42.4, 25.8, 22.2, 13.8; HRMS *m/z*: Calcd for $C_{15}H_{19}NO_5$: 293.1263; Found: 293.1260.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48. Found: C, 61.75; H, 6.54.

Methyl (±)-5,5-Dimethyl-2-(2-nitrophenyl)-4-oxohexanoate (16). 2.18 g (7.44 mmol, 92%); IR 1744, 1712, 1530, 1353 cm^{-1}; ^1H NMR δ 7.96 (d, J = 8.1 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 1 H), 4.66 (dd, J = 8.5, 4.8 Hz, 1 H), 3.66 (s, 1 H), 3.48 (dd, J = 18.1, 8.5 Hz, 1 H), 2.96 (dd, J = 18.1, 4.8 Hz, 1 H). 1.15 (s, 9 H); ^{13}C NMR δ 212.7, 172.5, 148.7, 133.6, 133.4, 130.7, 128.4, 125.2, 52.4, 44.0, 42.8, 40.3, 26.3 (3); HRMS *m/z*: Calcd for $C_{15}H_{19}NO_5$: 293.1263; Found: 293.1262.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48. Found: C, 61.69; H, 6.52.

Methyl (±)-2-(2-Nitrophenyl)-4-oxobutanoate (17). A solution of 1.50 g (6.38 mmol) of **8** in 150 mL of methanol was treated with ozone at –78 °C until TLC indicated that all of the starting material had been consumed. The reaction was quenched at –78 °C by adding 6.49 g (7.70 mL, 108.5 mmol) of dimethyl sulfide and 260 mg of *p*-

toluenesulfonic acid. The reaction mixture was stirred and allowed to warm to room temperature over 8 h, then concentrated under reduced pressure. The resulting yellow oil was diluted with ether, washed with $NaHCO_3$ (2x) and NaCl (1x), and dried ($MgSO_4$). Vacuum filtration followed by concentration under reduced pressure gave a mixture of aldehyde **17** and acetal **18**. This mixture was dissolved with 75 mL of tetrahydrofuran and cooled to 0 °C. To the resulting solution, 75 mL of a 3% aqueous solution of $HClO_4$ was added dropwise, and the reaction was stirred at 0 °C for 1 h and at room temperature for 6 h. The solution was extracted with methylene chloride (2x) and the combined organic layers were washed with $NaHCO_3$ (2x) and NaCl (1x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure to yield 1.48 g (6.24 mmol, 98%) of **17** which was used without further purification. IR 2846, 2733, 1744, 1729, 1527, 1354 cm^{-1}; ^1H NMR δ 9.80 (s, 1 H), 8.00 (dd, J = 7.8, 1.4 Hz, 1 H), 7.58 (td, J = 7.7, 1.4 Hz, 1 H), 7.47 (m, 2 H), 4.76 (dd, J = 8.1, 5.1 Hz, 1 H), 3.65 (s, 1 H), 3.55 (dd, J = 18.7, 8.1 Hz, 1 H), 2.97 (dd, J = 18.7, 5.1 Hz, 1 H); ^{13}C NMR δ 198.5, 171.8, 148.7, 133.6, 132.9, 130.9, 128.7, 125.4, 52.7, 46.6, 41.4; HRMS *m/z*: Calcd for $C_{11}H_{11}NO_5$: 237.0637; Found: 237.0636.

Representative Procedure for Reduction-Reductive Amination: Methyl (±)-(2*R,4*S**)-2-Methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (19).** To a solution containing 750 mg (2.99 mmol) of **13** in 125 mL of methanol was added 190 mg of 5% palladium-on-carbon. The mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atm of hydrogen at 30 °C for 2.5 h. The crude reaction mixture was concentrated, diluted with diethyl ether, and vacuum filtered through a pad of Celite topped with a layer of $MgSO_4$ to remove the catalyst. The filtrate was concentrated under

vacuum to yield 600 mg (2.93 mmol, 98%) of **19** as a light yellow oil that crystallized on standing at –20 °C. The resulting solid was triturated with 3% ether in hexanes to give **19** as an off white powder, mp 82-84 °C. IR 3395, 1737 cm^{-1}; ^1H NMR δ 7.01 (t, J = 8.1 Hz, 1 H), 6.97 (d, J = 7.7 Hz, 1 H), 6.64 (t, J = 7.7 Hz, 1 H), 6.50 (d, J = 8.1 Hz, 1 H), 3.96 (dd, J = 12.0, 5.9 Hz, 1 H), 3.76 (br s, 1 H), 3.76 (s, 3 H), 3.41 (m, 1 H), 2.15 (ddd, J = 12.8, 5.9, 2.6 Hz, 1 H), 1.95 (dd, J = 22.9, 12.8 Hz, 1 H), 1.23 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 175.0, 144.7, 128.1, 127.3, 117.9, 117.6, 114.7, 52.0, 46.3, 43.9, 34.4, 22.3; HRMS *m/z*: Calcd for $C_{12}H_{15}NO_2$: 205.1103; Found: 205.1104.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.29; H, 7.33; N, 6.76.

Methyl (±)-(2*R, 4*S**) -2- Phenyl-1, 2, 3, 4-tetrahydroquinoline-4-carboxylate (20).** 619 mg (2.32 mmol, 97%); mp 75-78 °C; IR 3395, 1736 cm^{-1}; ^1H NMR δ 7.45-7.27 (complex, 5 H), 7.07 (t, J = 8.1 Hz, 1 H), 7.03 (d, J = 7.7, 1 H), 6.72 (t, J = 7.7 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 4.42 (dd, J = 10.2, 3.7 Hz, 1 H), 4.11 (dd, J = 11.1, 6.5 Hz, 1 H), 4.10 (br s, 1 H), 3.71 (s, 3 H), 2.36 (m, 2 H); ^{13}C NMR δ 174.5, 144.7, 143.2, 128.7, 128.3, 128.1, 127.9, 126.7, 117.8, 117.7, 114.9, 55.7, 52.0, 44.1, 35.2; HRMS *m/z*: Calcd for $C_{17}H_{17}NO_2$: 267.1259; Found: 267.1259.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.33; H, 7.33; N, 5.29.

Methyl (±)-(2*R,4*S**)-2-Butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (21).** 625 mg (2.53 mmol, 99%); mp 53-54 °C; IR 3393, 1736 cm^{-1}; ^1H NMR δ 7.02 (t, J = 8.1 Hz, 1 H), 6.96 (d, J = 7.7 Hz, 1 H), 6.64 (t, J = 7.7 Hz, 1 H), 6.51 (d, J = 8.1 Hz, 1 H), 3.94 (dd, J = 11.8, 5.7 Hz, 1 H), 3.80 (br s, 1 H), 3.76 (s, 3 H), 3.26 (m, 2 H), 2.21

(ddd, J = 12.6, 5.7, 2.5 Hz, 1 H), 1.94 (dd, J = 23.6, 11.0 Hz, 1 H), 1.52 (m, 2 H), 1.38 (m, 4 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 175.0, 144.6, 128.1, 127.9, 118.1, 117.4, 114.7, 52.0, 50.7, 43.9, 36.1, 32.5, 27.6, 22.7, 14.0; HRMS *m/z*: Calcd for $C_{15}H_{21}NO_2$: 247.1572; Found: 247.1571.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 73.06; H, 8.52; N, 5.72.

Methyl (±)-(2*R,4*S**)-2-*tert*-Butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (22).** 588 mg (2.38 mmol, 93%); mp 76-79 °C; IR 3381, 1736 cm^{-1}; ^{1}H NMR δ 7.02 (t, J = 8.0 Hz, 1 H), 6.93 (d, J = 7.7 Hz, 1 H), 6.62 (t, J = 7.6 Hz, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 3.93 (dd, J = 12.5, 5.3 Hz, 1 H), 3.84 (br s, 1 H), 3.78 (s, 3 H), 3.00 (dd, J = 11.5, 2.3 Hz, 1 H), 2.20 (ddd, J = 12.5, 5.3, 2.3 Hz, 1 H), 1.93 (dd, J = 24.0, 11.5 Hz, 1 H), 0.98 (s, 9 H); ^{13}C NMR δ 175.2, 145.2, 127.9, 127.7, 118.2, 117.3, 114.8, 59.8, 52.0, 44.4, 33.3, 27.7, 25.8 (3); HRMS *m/z*: Calcd for $C_{15}H_{21}NO_2$: 247.1572; Found: 247.1568.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 73.08; H, 8.53; N, 5.65.

Methyl (±)-1,2,3,4-Tetrahydroquinoline-4-carboxylate (23). 400 mg (2.09 mmol, 90%); IR 3403, 1729 cm^{-1}; ^{1}H NMR δ 7.10 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 6.63 (t, J = 7.8 Hz, 1 H), 6.51 (d, J = 8.0 Hz, 1 H), 3.78 (t, J = 4.8 Hz, 1 H), 3.71 (s, 3 H), 3.69 (br s, 1 H), 3.43 (td, J = 11.0, 3.2 Hz, 1 H), 3.27 (dt, J = 11.5, 4.8 Hz, 1 H), 2.27 (m, 1 H); ^{13}C NMR δ 174.9, 144.5, 130.3, 128.1, 117.0 (2), 114.8, 52.0, 41.5, 38.7, 24.4; HRMS *m/z*: Calcd for $C_{11}H_{13}NO_2$: 191.0946; Found: 191.0943.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.32. Found: C, 69.29; H, 6.85; N, 7.41.

Alternative Procedure for the Alkylation of Methyl (2-Nitrophenyl) acetate (2): Methyl (±)-2-(2-Nitrophenyl)-4-oxopentanoate (13). The general procedure of Makosza and Tyrala[34] was used. A 250-mL, three-necked, round-bottomed flask containing a magnetic stir bar was charged with 75 mL of dry acetonitrile, 12 mg of 18-crown-6, and 11.6 g (84 mmol) of anhydrous potassium carbonate. Stirring was initiated and 1.95 g (10 mmol) of **2** was added. To the resulting blue solution, was added 1.16 g (12.5 mmol) of chloroacetone and the solution was stirred at 30 °C. The reaction progress was monitored by TLC. After 24 h, TLC indicated that the reaction was proceeding slowly and 0.25 g (1.67 mmol) of sodium iodide was added. An additional 3.25 g (35.2 mmol) of chloroacetone was added was added over a 12-day period. After 12 days, the reaction mixture was vacuum filtered, diluted with ether, washed with $Na_2S_2O_3$ (3x) and NaCl (2x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-20%) to yield 2.79 g (11.1 mmol, 56%) of **13** as a light yellow oil. The spectral data matched those reported above.

Attempted Alternative for the Alkylation of Methyl (2-Nitrophenyl)acetate (2): Methyl (±)-2-(2-Nitrophenyl)-4-oxo-4-phenylpentanoate (14). The general procedure of Makosza and Tyrala[34] was used. A 250-mL, three-necked, round-bottomed flask containing a magnetic stir bar was charged with 75 mL of dry acetonitrile, 12 mg of 18-crown-6, and 11.6 g (84 mmol) of anhydrous potassium carbonate. Stirring was

initiated and 1.95 g (10 mmol) of **2** was added. To the resulting blue solution, was added a solution of 2.03 g (13.1 mmol) of phenacyl chloride in 10 mL of dry acetonitrile and the solution was stirred at 30 °C. The reaction progress was monitored by TLC. After 24 h, TLC indicated that the reaction was proceeding slowly and 0.50 g (3.34 mmol) of sodium iodide was added. An additional 0.60 g (3.9 mmol) of sodium iodide was added over 3 days. Further TLC indicated that no product was being formed.

Representative Ozonolysis and Reduction-Reductive Amination Procedure: Methyl (2*R,4*S**)-1,2-Dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (24).** A solution containing 500 mg (2.01 mmol) of **9** in 125 mL of methanol was cooled to –78 °C and treated with ozone until TLC showed that all of the starting material was consumed. The crude reaction mixture was transferred to a stainless steel hydrogenation vessel. To the mixture was added 0.50 mL of 37% aqueous formaldehyde (54.5 mg, 18.2 mmol of HCHO) and 125 mg of 5% palladium-on-carbon. The mixture was hydrogenated under 4 atm of hydrogen for 6 h at 30 °C. Following hydrogenation, the reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite topped with a layer $MgSO_4$ to remove the catalyst. Concentration gave a yellow oil that was flash chromatographed on a 30 cm x 2 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-20%). The major band yielded 352 mg (1.61 mmol, 80%) of **24** as a light yellow oil that darkened upon exposure to air. IR 1744 cm^{-1}; ^1H NMR δ 7.15 (tm, J = 7.4 Hz, 1 H), 7.00 (dm, J = 7.4 Hz, 1 H), 6.65 (td, J = 7.4, 1.2 Hz, 1 H), 6.62 (d, J = 7.4 Hz, 1 H), 3.79 (t, J = 6.4 Hz, 1 H), 3.74 (s, 3 H), 3.40 (sextet, J = 5.9 Hz, 1 H), 2.88 (s, 3 H), 2.26 (m, 2 H), 1.13 (d, J = 6.5 Hz, 1 H): ^{13}C

NMR δ 174.8, 145.5, 139.1, 128.2, 119.1, 116.0, 119.9, 52.9, 52.0, 41.9, 36.5, 32.7, 18.5; HRMS *m/z*: Calcd for $C_{13}H_{17}NO_2$: 219.1259; Found: 219.1257.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.51; H, 7.80; N, 6.42.

Methyl (2*R,4*S**)-1-Methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (25)**. 330 mg (1.17 mmol, 73%); IR 1744 cm^{-1}; ^1H NMR δ 7.34-7.18 (complex, 6 H), 6.97 (d, *J* = 7.4 Hz, 1 H), 6.75 (d, *J* = 7.4 Hz, 1 H), 6.70 (t, *J* = 7.4 Hz, 1 H), 4.43 (dd, *J* = 7.6, 4.8 Hz, 1 H), 3.85 (dd, *J* = 8.1, 5.3 Hz, 1 H), 3.42 (s, 3 H), 2.80 (s, 3 H), 2.56 (dt, *J* = 13.3, 8.1 Hz, 1 H), 2.40 (dt, *J* = 13.3, 5.3 Hz, 1 H); ^{13}C NMR δ 173.8, 146.1, 142.5, 128.7, 128.5, 128.4, 127.7, 126.9, 119.5, 116.2, 111.6, 62.4, 51.8, 42.6, 37.8, 34.8; HRMS *m/z*: Calcd for $C_{18}H_{19}NO_2$: 281.1416; Found: 281.1415.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.59; H, 6.82; N, 4.90.

Methyl (2*R,4*S**)-2-Butyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (26)**. 341 mg (1.31 mmol, 76%); IR 1744 cm^{-1}; ^1H NMR δ 7.14 (tm, *J* = 7.4 Hz, 1 H), 6.96 (dm, *J* = 7.4 Hz, 1 H), 6.64 (td, *J* = 7.4, 1.2 Hz, 1 H), 6.59 (d, *J* = 7.5 Hz, 1 H), 3.74 (t, *J* = 6.3 Hz, 1 H), 3.73 (s, 3 H), 3.24 (m, 1 H), 2.91 (s, 3 H), 2.37 (dt, *J* = 13.6, 5.8 Hz, 1 H), 2.20 (ddd, *J* = 13.6, 6.3, 3.9 Hz, 1 H), 1.59 (m, 1 H), 1.36-1.19 (complex, 5 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 179.4, 145.4, 129.2, 128.2, 118.9, 115.7, 111.7, 58.0, 52.0, 41.6, 37.4, 31.4, 29.0, 27.8, 22.9, 14.1; HRMS *m/z*: Calcd for $C_{16}H_{23}NO_2$: 261.1729; Found: 261.1728.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.78; H, 8.85; N, 5.33.

Methyl (2*R,4*S**)-2-*tert*-Butyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (27).** 332 mg (1.27 mmol, 74%); IR 1744 cm^{-1}; ^1H NMR δ 7.14 (tm, J = 8.0 Hz, 1 H), 6.85 (dm, J = 7.6 Hz, 1 H), 6.72 (t, J = 7.8 Hz, 1 H), 6.68 (dd, J = 7.4, 1.1 Hz, 1 H), 3.82 (s, 3 H), 3.53 (dd, J = 12.0, 3.8 Hz, 1 H), 3.11 (s, 3 H), 3.04 (dd, J = 10.0, 7.7 Hz, 1 H), 2.34 (ddd, J = 13.4, 7.7, 3.8 Hz, 1 H), 2.03 (ddd, J = 13.4, 12.0, 10.0 Hz, 1 H), 0.91 (s, 9 H); ^{13}C NMR δ 174.4, 149.1, 127.8, 127.5, 124.5, 117.9, 117.3, 67.6, 51.8, 44.8, 42.8, 38.3, 32.2, 27.6 (3); HRMS *m/z*: Calcd for $C_{16}H_{23}NO_2$: 261.1729; Found: 261.1725.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.51; H, 8.84; N, 5.51.

Methyl (±)-3-(1-Cyclopentenyl)-2-(2-nitrophenyl)propanoate (30). The general procedure of Makoska and Tyrala[34] was used. A 250 mL, three-necked, round-bottomed flask was charged with 95 mL of acetonitrile, 24.0 g (174 mmol) of anhydrous potassium carbonate, and 20 mg of 18-crown-6. Stirring was started and 2.93 g (15 mmol) of **2** was added . The reaction turned a deep blue, and 5.35 g (24.0 mmol) of **28** was added. The mixture was stirred at reflux for approximately 18 h. The solids were removed by vacuum filtration and the filtrate was concentrated under reduced pressure. The resulting oil was flash chromatographed on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-15%) to yield 2.73 g (9.92 mmol, 66%) of **30** as a light yellow oil. IR 1737, 1654, 1530, 1353 cm^{-1}; ^1H NMR δ 7.86 (d, J = 8.1 Hz, 1 H), 7.57 (dd, J = 4.9, 1.1 Hz, 2 H), 7.40 (m, 1 H), 5.29 (m, 1 H), 4.45 (t, J = 7.4 Hz, 1 H), 3.67 (s, 3 H), 2.93 (dd, J = 15.5, 7.6 Hz, 1 H), 2.61 (dd, J = 15.5, 7.2 Hz, 1 H), 2.25-2.17 (complex, 4 H), 1.80 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR

δ 173.0, 149.4, 140.5, 133.3, 132.8, 129.8, 128.0, 126.7, 124.6, 52.3, 44.7, 35.0, 34.5, 32.5, 23.5; HRMS *m/z*: Calcd for $C_{15}H_{17}NO_4$: 275.1157; Found: 275.1154.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18. Found: C, 65.69; H, 6.22.

Methyl (±)-3-(2-Methyl-1-cyclopentenyl)-2-(2-nitrophenyl)propanoate (31). 3.91 g (13.5 mmol, 82%); IR 1738, 1530, 1353 cm^{-1}; ^1H NMR δ 7.85 (d, J = 8.0 Hz, 1 H), 7.56 (dd, J = 4.9, 1.2 Hz, 2 H), 7.40 (m, 1 H), 4.38 (dd, J = 8.5, 6.6 Hz, 1 H), 3.68 (s, 3 H), 2.85 (dd, J = 13.5, 6.6 Hz, 1 H), 2.61 (dd, J = 13.5, 8.5 Hz, 1 H), 2.22-2.10 (complex, 4 H), 1.68 (m, 2 H), 1.36 (s, 3 H); ^{13}C NMR δ 173.1, 149.5, 135.4, 133.5, 132.7, 130.6, 130.3, 127.9, 124.5, 52.3, 44.6, 38.3, 35.7, 32.4, 21.6, 13.5; HRMS *m/z*: Calcd for $C_{16}H_{19}NO_4$: 289.1314; Found: 289.1313.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.44; H, 6.57. Found: C, 66.71; H, 6.60.

Methyl (±)-2-(2-Nitrophenyl)-4,8-dioxooctanoate (32). A solution of 600 mg (2.18 mmol) of **30** in 150 mL of methanol was treated with ozone at –78 °C until TLC indicated that all of the starting material had been consumed. The reaction mixture was treated with dimethyl sulfide and *p*-toluenesulfonic acid as previously described. The reaction mixture was stirred and allowed to warm to room temperature over 12 h and then concentrated under reduced pressure. The resulting yellow oil was diluted with ether, washed with $NaHCO_3$ (2x) and NaCl (1x), and dried ($MgSO_4$). Vacuum filtration followed by concentration under reduced pressure gave a mixture of keto aldehyde **32** and ketoacetal **33**. The mixture was dissolved in tetrahydrofuran and an equal volume of 3% aqueous $HClO_4$ was added at 0 °C. The reaction was stirred at 0 °C for 1 h and at room temperature for 3 h. The solution was extracted with methylene chloride (2x). The organic layer was washed with $NaHCO_3$ (2x) and NaCl (1x), dried ($MgSO_4$), vacuum

filtered, and concentrated under reduced pressure to yield 626 mg (2.04 mmol, 94%) of **32**, which was used without further purification: IR 2840, 2733, 1744, 1730, 1530, 1353 cm^{-1}; ^1H NMR δ 9.75 (t, J = 1.4 Hz, 1 H), 7.97 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.59 (td, *J* = 7.4, 1.4 Hz, 1 H), 7.45 (m, 2 H), 4.71 (dd, *J* = 8.8, 4.5 Hz, 1 H), 3.65 (s, 3 H), 3.42 (dd, *J* = 17.9, 8.8 Hz, 1 H), 2.82 (dd, *J* = 17.9, 4.5 Hz, 1 H), 2.66-2.43 (complex, 4 H), 1.92 (quintet, *J* = 7.0 Hz, 2 H); ^{13}C NMR δ 206.6, 201.7, 172.1, 148.5, 133.5, 133.2, 130.8, 128.4, 125.2, 52.4, 45.3, 42.7, 41.2, 30.2, 15.9; HRMS *m/z*: Calcd for $C_{15}H_{17}NO_6$: 307.1055; Found: 307.1052.

Methyl (±)-(4a*R,6*S**)-2,3,4,4a,5,6-Hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate (34).** To a solution of 550 mg (1.79 mmol) of **32** in 150 mL of methanol was added 200 mg of 5% palladium-on-carbon. The mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atm of hydrogen at 30 °C for 2.5 h. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite topped with a layer $MgSO_4$ to remove the catalyst. Concentration of the filtrate under vacuum yielded a light yellow oil that crystallized on standing. Recrystallization from pentane gave 303 mg (1.24 mmol, 69%) of **34** as light yellow crystals, mp 68-70 °C. IR 1744 cm^{-1}; ^1H NMR δ 7.13 (tm, J = 7.7 Hz, 1 H), 6.96 (dm, *J* = 7.7 Hz, 1 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 6.69 (t, *J* = 8.1 Hz, 1 H), 3.91 (m, 2 H), 3.74 (s, 3 H), 2.85 (m, 1 H), 2.56 (td, *J* = 12.2, 2.7 Hz, 1 H), 2.16 (m, 2 H), 1.77 (m, 3 H), 1.64 (m, 1 H), 1.39 (m, 2 H); ^{13}C NMR δ 174.9, 146.9, 128.1 (2), 121.5, 117.8, 113.4, 55.4, 52.0, 47.9, 43.9, 34.0, 33.5, 25.8, 24.0; HRMS *m/z*: Calcd for $C_{15}H_{19}NO_2$: 245.1416; Found: 245.1418.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.66; H, 7.79; N, 5.76.

Methyl (±)-2-(2-Nitrophenyl)-4,8-dioxononanoate (35). A solution of 1.00 g (3.46 mmol) of **31** in 150 mL of methanol was cooled to –78 °C and treated with ozone until TLC indicated that all of the starting material was consumed. The ozonolysate was treated with 10.0 g (8.46 mL, 136 mmol) of dimethyl sulfide and 250 mg of *p*-toluenesulfonic acid, and subsequently warmed to room temperature over 12 h. The reaction mixture was concentrated under vacuum and diluted with ether. The solution was washed with $NaHCO_3$ (2x) and NaCl (1x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure. The resulting oil was flash chromatographed on a 30 cm x 2.5 cm silica gel column using increasing concentrations of ether in hexanes (5-20%) to yield 1.06 g (3.29 mmol, 95%) of **35** as a yellow oil that crystallized upon standing, mp 47-48 °C. IR 1744, 1715, 1530, 1353 cm^{-1}; ^1H NMR δ 7.97 (dd, J = 8.0, 1.5 Hz, 1 H), 7.59 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.44 (m, 2 H), 4.70 (dd, *J* = 8.8, 4.5 Hz, 1 H), 3.66 (s, 3 H), 3.42 (dd, *J* = 17.9, 8.8 Hz, 1 H), 2.82 (dd, *J* = 17.9, 4.5 Hz, 1 H), 2.62-2.41 (complex, 4 H), 2.13 (s, 3 H), 1.86 (quintet, *J* = 7.0 Hz, 2 H); ^{13}C NMR δ 208.3, 207.1, 172.2, 148.6, 133.5, 133.3, 130.8, 128.4, 125.2, 52.5, 45.3, 42.7, 42.2, 41.3, 29.9, 17.5; HRMS *m/z*: Calcd for $C_{16}H_{19}NO_6$: 321.1212; Found: 321.1208.

Methyl (±)-(1*R ,4a*R**, 6*S**)-1–Methyl -2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]-quinolizine-6-carboxylate (36).** To a solution of 500 mg (1.56 mmol) of **35** in 150 mL of methanol was added 200 mg of 5% palladium-on-carbon. The mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atm of hydrogen at 30 °C for 3 h. The crude reaction mixture was concentrated, diluted with ether, and vacuum

filtered through a pad of Celite topped with a layer of $MgSO_4$ to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by PTLC using 50% ether in hexanes. The main band gave 242 mg (0.93 mmol, 60%) of **36** as a light yellow oil that crystallized upon standing, mp 36-38 °C. IR 1744 cm^{-1}; ^1H NMR δ 7.13 (t, J = 7.5 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.67 (m, 2 H), 3.84 (dd, J = 9.5, 5.8 Hz, 1 H), 3.71 (s, 3 H), 3.53 (m, 1 H), 3.19 (m, 1 H), 2.17-1.94 (complex, 3 H), 1.80 (m, 2 H), 1.65 (m, 1 H), 1.57 (m, 2 H), 1.23 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 175.0, 146.4, 127.8, 127.4, 123.3, 116.9, 112.7, 52.3, 51.9, 49.9, 44.2, 35.1, 31.1, 29.5, 20.9, 18.0; HRMS *m/z*: Calcd for $C_{16}H_{21}NO_2$: 259.1572; Found: 259.1571.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.36; H, 8.15; N, 5.39.

Two other minor bands isolated from the PTLC gave the following compounds:

Methyl (8*S, 9*S**)- 8 -Methyl- 5, 6, 7, 8, 8a, 9, 10, 10a-octahydroacridine- 9 - carboxylate (37).** 24 mg (0.093 mmol, 6%); mp 91-93 °C; IR 3374, 1730 cm^{-1}; ^1H NMR δ 7.15 (dm, J = 7.7 Hz, 1 H), 7.02 (tm, J = 7.7 Hz, 1 H), 6.65 (dt, J = 7.6, 1.2 Hz, 1 H), 6.53 (dd, J = 8.0, 1.2 Hz, 1 H), 3.69 (s, 3 H), 3.58 (d, J = 9.8 Hz, 1 H), 3.38 (br s, 1 H), 2.73 (td, J = 10.6, 3.9 Hz, 1 H), 1.93 (q, J = 10.0 Hz, 1 H), 1.87 (m, 1 H), 1.78 (m, 1 H), 1.67 (dm, J = 12.8 Hz, 1 H), 1.43 (tm, J = 9.4 Hz, 1 H), 1.40-1.09 (complex, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 176.0, 145.2, 127.7, 127.6, 119.6, 118.2, 115.0, 54.5, 52.0, 48.8, 47.7, 37.6, 35.4, 33.1, 23.9, 18.8; HRMS *m/z*: Calcd for $C_{16}H_{21}NO_2$: 259.1573; Found: 259.1576.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.35; H, 8.14; N, 5.34.

Methyl (2*R,4*S**)-2-(4-Oxopentyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (38).** 9 mg (0.033 mmol, 2%); IR 3388, 1740 cm^{-1}; ^1H NMR δ 7.02 (tm, J = 7.7 Hz, 1 H), 6.96 (dm, J = 7.7 Hz, 1 H), 6.64 (dt, J = 7.7, 1.2 Hz, 1 H), 6.52 (dd, J = 8.0, 1.2 Hz, 1 H), 3.93 (dd, J = 11.7, 5.8 Hz, 1 H), 3.76 (s, 3 H), 3.69 (dd, J = 10.5, 4.4 Hz, 1 H), 3.26 (m, 1 H), 2.50 (t, J = 7.1 Hz, 1 H), 1.20 (dd, J = 5.8, 2.6 Hz, 1 H), 2.16 (m, 1 H), 2.15 (s, 3 H), 1.98 (quintet, J = 11.7 Hz, 1 H), 1.74 (m, 2 H), 1.52 (m, 2 H); ^{13}C NMR δ 208.5, 174.9, 144.5, 128.1, 128.0, 118.1, 117.6, 114.8, 52.0, 50.4, 43.7, 43.3, 35.7, 32.3, 30.0, 19.3; HRMS *m/z*: Calcd for $C_{16}H_{21}NO_3$: 275.1521; Found: 275.1522.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.63; N, 5.09. Found: C, 70.11; H, 7.67; N, 5.18.

Acknowledgements. Support of this work by the NIH (GM54256) and by the Oklahoma Center for the Advancement of Science and Technology (HR01-015) was greatly appreciated. The authors wish to thank Professor E. J. Eisenbraun for a generous sample of 2,3,3-trimethylbutene used for the preparation of **6**. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

CHAPTER III

DIASTEREOSELECTIVE SYNTHESIS OF 2,5-DISUBSTITUTED 2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINES BY A TANDEM REDUCTION-REDUCTIVE AMINATION

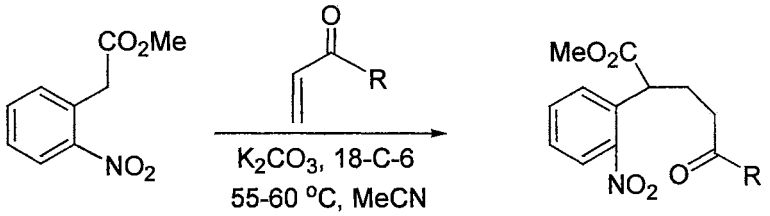
Introduction

Certain tetrahydro-1*H*-1-benzazepine derivatives have been found to selectively inhibit specific receptors of the hormone arginine vasopressin (AVP). AVP exerts its actions through two receptor subtypes, V_{1a} and V_2, which play a role in the regulation of renal and cardiovascular functions. The control of blood pressure, blood volume, and plasma osmolality are mediated by AVP V_2 receptors in the kidneys. Inhibitors of the AVP V_2 receptor may have applications as treatments for disorders such as diabetes, congestive heart failure, and hypertension.[35]

Previous work by Bunce and co-workers demonstrated the use of the reduction-reductive amination reaction for the synthesis of 2,4-disubstituted-1,2,3,4-tetrahydroquinolines. The tandem reduction-reductive amination sequence producing the 2,4-disubstituted-1,2,3,4-tetrahydroquinolines was highly diastereoselective, resulting in the exclusive formation of cis products. Application of this method to the synthesis of larger ring systems was investigated to determine if the diastereoselectivity of the reduction-reductive amination was maintained. The reduction-reductive amination

method has thus been extended to the synthesis of 2,5-disubstituted-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives.

Synthesis of Cyclization Substrates. The synthesis of **1** is shown in Figure 18. Alkylation of **1** with various vinyl ketones, **2-5**, in dry acetonitrile at 55-60 °C containing potassium carbonate and a catalytic amount of 18-crown-6[34] produced esters **6-9** (Figure 32). The yields of the alkylations ranged from 71% to 94% and are summarized in Table IV.



1

2 R = Me
3 R = Et
4 R = Ph
5 R = OMe

6 R = Me
7 R = Et
8 R = Ph
9 R = OMe

Figure 32. Alkylation of methyl (2-nitrophenyl)acetate (**1**) with vinyl ketones **2-5**.

TABLE IV

THE ALKYLATION OF METHYL (2-NITROPHENYL) ACETATE WITH VINYL KETONES

starting vinyl ketone	R	Product	yield (%)
2	Me	**6**	91
3	Et	**7**	94
4	Ph	**8**	90
5	OMe	**9**	71

The synthesis of nitroaldehyde **12** is shown in Figure 33. Alkylation of **1** with 4-iodo-1-butene in acetonitrile at 55-60 °C containing postassium carbonate and a catalytic amount of 18-crown-6 gave alkene **10** in 59% yield. Ozonolysis of **10** in methanol at –78 °C followed by reductive workup with dimethyl sulfide and *p*-TsOH produced acetal **11** containing 5-10% of aldehyde **12**. Conversion of acetal **11** to the aldehyde **12** was accomplished in 94% yield by treatment with a 1:1 mixture of a 3% aqueous solution of $HClO_4$ and tetrahydrofuran.

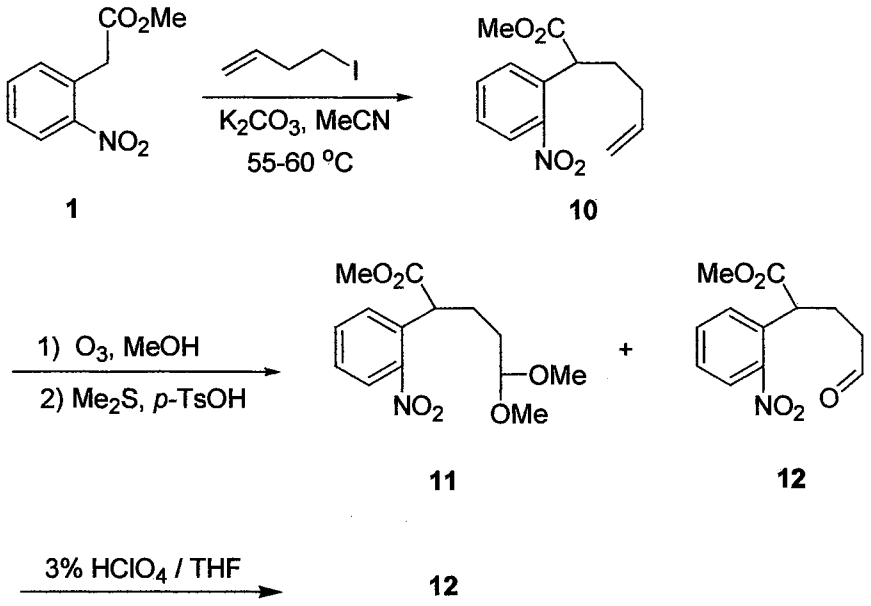
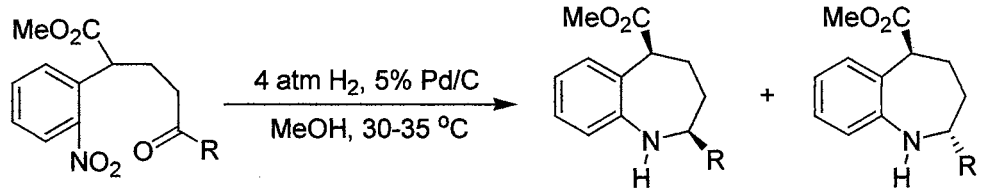


Figure 33. Synthesis of nitroaldehyde **12**.

Synthesis of 2,5-Disubstituted 2,3,4,5-Tetrahydro-1*H*-1-benzazepines. The reduction-reductive amination of compounds **6** and **7** are illustrated in Figure 34. Reduction of **6** and **7** under 4 atm of hydrogen in methanol at 30-35 °C using 5% palladium-on-carbon catalyst produced both the cis and trans products, in overall yields

of 98% (**13** and **14**) and 73% (**15** and **16**). The cis:trans ratio for products **13** and **14** was 11:1; the cis:trans ratio of **15** and **16** was 8:1. The structure of **13** was confirmed with X-ray crystallographic data (Plate IV).



6 R = Me
7 R = Et

13 R = Me
15 R = Et

14 R = Me
16 R = Et

Figure 34. Tandem reduction-reductive amination forming cis and trans products.

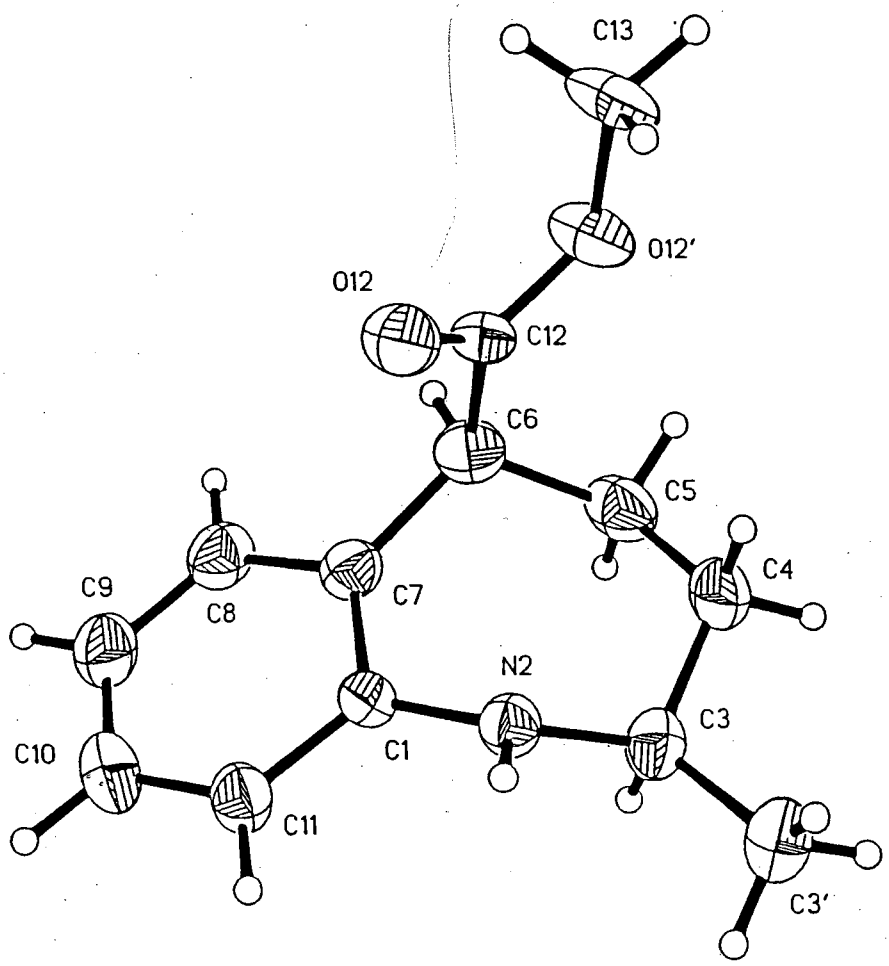


Plate IV. X-ray structure of Methyl (±)-(2*R**,5*S**)-2-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**13**).

Reduction-reductive amination of the phenyl-susbstituted substrate **8** under 4 atm of hydrogen in methanol at 30-35 °C using 5% palladium-on-carbon catalyst gave a mixture of compounds, with the major product being amide **17** in 31% yield. Analysis of the two other bands revealed the expected products **18** and **19** in yields of 16% and 3% respectively (Figure 35). Catalytic hydrogenation at 1.5-2 atm of hydrogen and 20 °C did not improve the yield of products **18** and **19**.

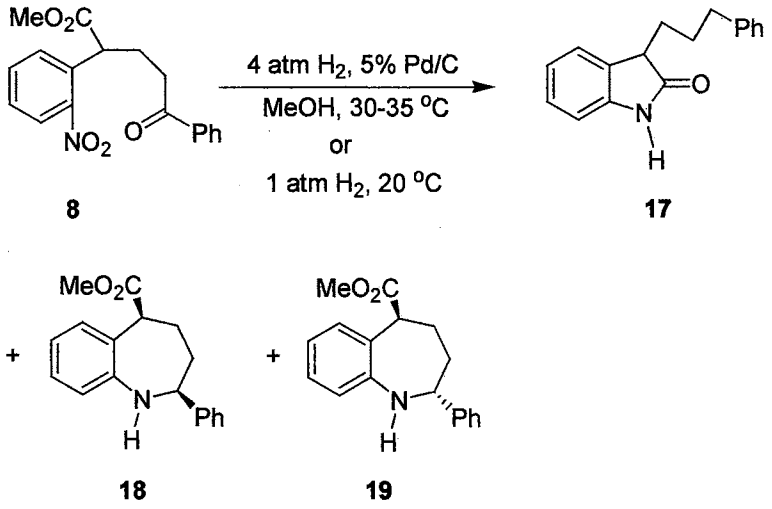


Figure 35. Tandem reduction-reductive amination of nitrophenylketone **8** forming a mixture of products.

Catalytic hydrogenation of diester **9** resulted in the formation of the uncyclized derivative **20** in 97% yield. Cyclization of **20** was accomplished by heating in benzene at 50 °C to give lactam **21** in 76% yield. The catalytic hydrogenation of diester **9** and subsequent cyclization are shown in Figure 36.

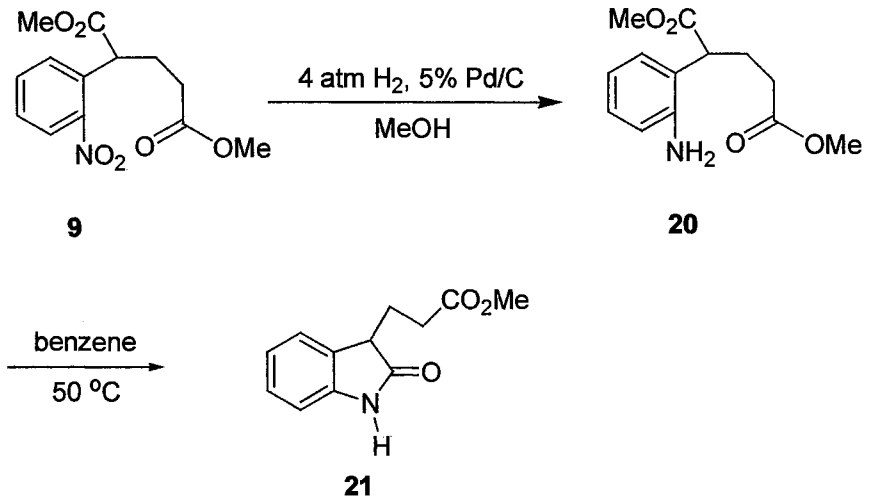


Figure 36. Catalytic hydrogenation of diester **9** and subsequent cyclization.

The synthesis of methyl 2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**22**) is shown in Figure 37. Reduction-reductive amination of **12** in methanol at 30-35 °C using 5% palladium-on-carbon catalyst produced **22** in 60% yield.

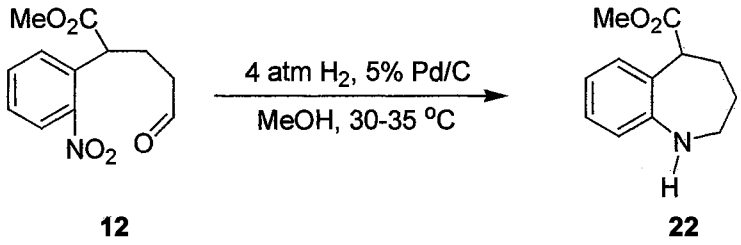


Figure 37. Synthesis of methyl 2,3,4,5-tetrahydro-1*H*-1-benzazepine-5- carboxylate **22**.

Discussion. As demonstrated previously for the synthesis of 2,4-disubstituted 1,2,3,4-tetrahydroquinolines, the major product is cis. The diastereoselectivity of the reduction-reductive amination arises from the addition of a hydrogen molecule to the face opposite the methyl ester in the final imine intermediate (Figure 28 in Chapter II). In the reduction-reductive amination producing the 2,5-disubstituted 2,3,4,5-tetrahydro-1*H*-1-

benzazepine products **13-16**, the reaction was also diastereoselective for the cis isomer (11:1 for **13** and **14**, 8:1 for **15** and **16**) but to a lesser degree than observed for the tetrahydroquinolines. The exact order of steps is unknown, but the reaction sequence likely begins with reduction of the aromatic nitro group to give amine **23** or the *N*-hydroxylamine (Figure 38). Condensation of the reduced nitrogen intermediate with the carbonyl followed by dehydration produces imine **24**. The double bond of **24** possesses two diastereotopic faces, one of which is partially blocked by the methyl ester. In comparison to the six-membered ring closures required to prepare tetrahydroquinolines, the methyl ester of imine **24** is further away from the double bond being reduced and the ring is more conformationally mobile. In one possible conformation of **24**, the ester group is in a pseudo-equatorial position. The greater distance from the double bond and pseudo-equatorial placement of the ester substituent makes it less effective at blocking the imine double bond to hydrogenation. This results in the production of trans minor products **14** and **16** in significant quantities. Tandem reduction-reductive amination was also employed successfully to synthesize the monosubstituted 2,3,4,5-tetrahydro-1*H*-1-benzazepine **22**.

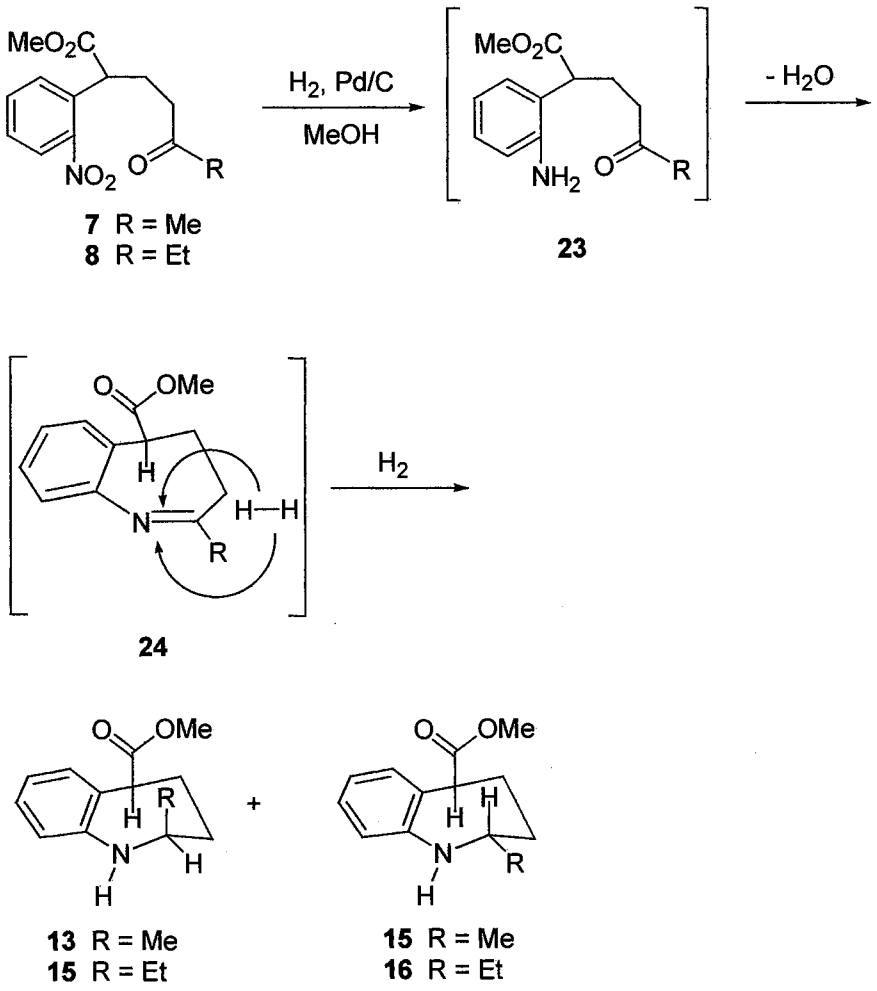
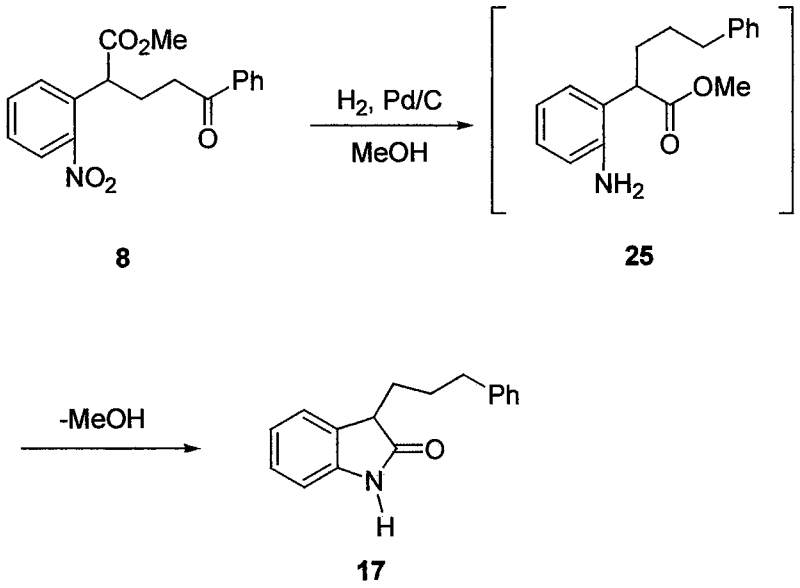


Figure 38. Proposed mechanism of the tandem reduction-reductive amination.

Catalytic hydrogenation of nitrophenylketone **8** under 4 atm of hydrogen in methanol at 30-35 °C produced amide **17** as the major product (Figure 39). This product likely results from reduction of the nitro group and hydrogenolysis of the ketone carbonyl forming intermediate **25**, followed by cyclization to give the lactam product. The formation of minor benzazepine products **18** and **19** arises from reduction of the nitro group and subsequent cyclization with an intact phenyl ketone in a manner similar to that mentioned for products **13-16**. Hydrogenolysis of a phenyl ketone has been observed at 1 atm of hydrogen in ethanol at 20 °C using a 5% palladium-on-carbon catalyst.[36]

Catalytic hydrogenation of nitrophenylketones resulting in hydrogenolysis of the phenyl carbonyl group has been demonstrated at temperatures of 40-50 °C, whereas reductive cyclization occurred when the reaction was carried out at 20 °C.[17] Catalytic hydrogenation of **8** under 1.5-2 atm hydrogen at 20 °C did not increase the yields of benzazepine products **18** and **19**.



8 **25** **17**

Figure 39. Hydrogenolysis of nitrophenylketone **8** prior to cyclization resulting in the formation of **17**.

Catalytic hydrogenation of diester **9** resulted in the formation of uncyclized **20** (Figure 36). The cyclization of **20** to lactam **21** occurred upon heating in benzene at 50 °C. In accordance with expected entropic considerations, formation of a 5-membered ring occurred in preference to the formation of a 7-membered ring.[37] The formation of the five-membered ring product is consistent with previous observations that five- and six-membered ring closures of carbocycles[37] and heterocycles are entropically favored over the formation of larger rings.[38]

Conclusion. This work represents the application of the tandem reduction-reductive amination approach to the diastereoselective production of 2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters; the unsubstituted tetrahydro-1*H*-1-benzazepine-5-carboxylic ester was also prepared. The diastereoselectivity derives from C5 ester group which directs the addition of hydrogen to the opposite side of the final imine intermediate. In these cases involving closure to benzazepine products, the blocking effect of the C5 ester was less effective than previously observed for closures to tetrahydroquinolines. Reductive cyclization of a nitrodiester to a lactam was also accomplished by the same catalytic hydrogenation conditions. Exclusive formation of the five membered ring lactam was observed.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Potassium carbonate was ground into a fine powder, dried under vacuum for 24 h at 120 °C, and stored in an oven at 120 °C until needed. Methyl (2-nitrophenyl)acetate (**1**) was prepared the method of Marvel and co-workers.[33] Unsaturated carbonyl compounds **2**, **3**, and **5** were commercially available. Phenyl vinyl ketone **4** was prepared by the method of Reich and co-workers.[39] Commercially available 4-bromo-1-butene was converted to the iodide by treatment with sodium iodide in acetone.

All reactions were run under dry nitrogen and in oven-dried glassware. The HCl (0.2 M, 1 M, 2 M, and 6 M), NaOH (0.2 M and 1 M), $NaHCO_3$ (saturated), $Na_2S_2O_3$ (5%), and NaCl (saturated) used in various procedures were aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on silica gel GF plates (Analtech no. 21521) with UV detection, or (2) capillary GC (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50-300 °C. Preparative separations were performed by one of the following methods: (1) flash column chromatography on silica gel (grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies UV- 5) or (2) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Band elution for both methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and referenced to polystyrene. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using $(CH_3)_4Si$ as an internal standard. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Representative Procedure for Conjugate Addition Reactions: Methyl (±)-2-(2-Nitrophenyl)-5-oxohexanoate (6). The general procedure of Makosza and Tyrala[34] was adapted. A 250-mL, three-necked, round-bottomed flask containing a magnetic stir bar was charged with 50 mL of dry acetonitrile, 12 mg of 18-crown-6, and 11.6 g (84 mmol) of anhydrous potassium carbonate. Stirring was initiated and 1.95 g (10.0 mmol) of **1** was added. To the resulting blue solution was added 0.92 g (13.2 mmol, 1.1 mL) of **2** and the solution was stirred at 55-60 °C. The progress of the reaction was monitored by TLC. The reaction was stirred for a total of 48 h, allowed to cool to room temperature, and filtered to remove solids. The filtrate was diluted with ether, washed with $NaHCO_3$ (1x) and NaCl (1x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-15%) to yield 2.40 g (9.05 mmol, 91%) of **6** as a light yellow oil. IR 1744, 1716, 1530, 1360 cm^{-1}; ^1H NMR δ 7.89 (d, J = 8.1 Hz, 1 H), 7.61 (t, J = 7.1 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.44 (t, J = 7.1 Hz, 1 H), 4.18 (t, J = 7.3 Hz, 1 H), 3.66 (s, 3 H), 2.60-2.42 (complex, 3 H), 2.11 (m, 1 H), 2.12 (s, 3 H); ^{13}C NMR δ 207.3, 172.6, 149.5, 140.4, 133.2, 129.9, 128.3, 124.7, 52.3, 45.1, 41.1, 29.9, 26.6; HRMS *m/z*: Calcd for $C_{13}H_{15}NO_5$: 265.0950; Found: 265.0946.

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.83; H, 5.72; N, 5.30.

Methyl (±)-2-(2-Nitrophenyl)-5-oxoheptanoate (7). 2.62 g (9.39 mmol, 94%); IR 1739, 1722, 1530, 1360 cm^{-1}; ^1H NMR δ 7.89 (d, J = 8.1 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.52 (d, J = 7.9 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 1 H), 4.19 (t, J = 7.1 Hz, 1 H),

3.66 (s, 3 H), 2.57-2.36 (complex, 5 H), 2.14 (m, 1 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 210.1, 172.7, 149.4, 140.9, 133.2, 130.0, 128.3, 124.7, 52.3, 45.2, 39.7, 35.8, 26.7, 7.7; HRMS *m/z*: Calcd for $C_{14}H_{17}NO_5$: 279.1106; Found: 279.1105.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02. Found: C, 60.19; H, 6.15; N, 5.04.

Methyl (±)-2-(2-Nitrophenyl)-5-oxo-5-phenylpentanoate (8). 3.18 g (9.72 mmol, 90%); IR 1744, 1687, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.90 (t, J = 7.1 Hz, 2 H), 7.63-7.46 (complex, 3 H), 7.44-7.40 (complex, 4 H), 4.32 (t, J = 7.4 Hz, 1 H), 3.67 (s, 3 H), 3.07 (m, 2 H), 2.64 (m, 1 H), 2.30 (m, 1 H); ^{13}C NMR δ 198.8, 172.7, 149.4, 136.6, 133.3, 133.2, 133.1, 130.0, 128.6, 128.3, 128.0, 124.8, 52.3, 45.4, 36.3, 27.2; HRMS *m/z*: Calcd for $C_{18}H_{17}NO_5$: 327.7111; Found: 327.7109.

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found; C, 65.92; H, 5.18; N, 4.20.

Dimethyl (±)-2-(2-Nitrophenyl)pentanedioate (9). 1.99 g (7.08 mmol, 71%); IR 1744, 1530, 1360 cm^{-1}; ^{1}H NMR δ 7.91 (d, J = 8.2 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.52-7.41 (complex, 2 H), 4.27 (t, J = 7.3 Hz, 1 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 2.52 (m, 1 H), 2.37 (m, 2 H), 2.18 (m, 1 H); ^{13}C NMR δ 172.9, 172.5, 149.4, 133.2, 132.9, 129.9, 128.4, 124.9, 52.4, 51.7, 45.2, 31.8, 27.9; HRMS *m/z*: Calcd for $C_{13}H_{15}NO_6$: 281.0899; Found: 281.0897.

Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.37; H, 5.43; N, 5.05.

Alkylation of Methyl (2-Nitrophenyl) Acetate (1): Methyl (±)-2-(2-Nitrophenyl)-5-hexenoate (10). The general procedure of Makosza and Tyrala[34] was

used. A 250-mL, three-necked, round-bottomed flask containing a magnetic stir bar was charged with 100 mL of dry acetonitrile, 12 mg of 18-crown-6, and 11.6 g (84 mmol) of anhydrous potassium carbonate. Stirring was initiated and 1.95 g (10.0 mmol) of **1** was added. To the resulting blue solution was added 2.27 g (12.5 mmol) of 4-iodo-1-butene and the solution was stirred at 55-60 °C. The progress of the reaction was monitored by TLC. The reaction was stirred at 55-60 °C for a total of 18 h and then allowed to cool to room temperature. The reaction mixture was diluted with ether, vacuum filtered to remove solids, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes (5-15%) to yield 1.47 g (5.90 mmol, 59%) of **10** as a light yellow oil. IR 1735, 1528 cm^{-1}; ^1H NMR δ 7.88 (d, J = 8.1 Hz, 1 H), 7.62-7.52 (complex, 2 H), 7.42 (t, J = 7.0 Hz, 1 H), 5.77 (m, 1 H), 5.02 (m, 1 H), 4.98 (m, 1 H), 4.20 (t, J = 7.2 Hz, 1 H), 3.67 (s, 3 H), 2.28 (m, 1 H), 2.07 (m, 2 H), 1.93 (m, 1 H); ^{13}C NMR δ 173.1, 137.0, 133.5, 133.0, 129.9, 128.1, 124.7, 155.8, 100.0, 52.3, 45.4, 32.0, 31.6; HRMS *m/z*: Calcd for $C_{13}H_{15}NO_4$: 249.1001; Found: 249.1000.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.41; H, 6.01; N, 5.75.

Ozonolysis of Methyl (±)-2-(2-Nitrophenyl)-5-hexenoate (10): Methyl (±)-2-(2-Nitrophenyl)-5-oxopentanoate (12). A solution containing 1.20 g (4.82 mmol) of **10** and 125 mL of methanol was cooled to –78 °C and treated with ozone until TLC indicated that all of the starting material had been consumed. The reaction was quenched at –78 °C by adding of 5.08 g (6.00 mL, 84.9 mmol) of dimethyl sulfide and 200 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred, allowed to warm to room

temperature over 8 h, and concentrated under reduced pressure. The resulting solution was diluted with ether, washed with $NaHCO_3$ (1x) and NaCl (1x), and dried with $MgSO_4$. Vacuum filtration followed by concentration under reduced pressure gave a mixture of dimethyl acetal **11** containing a small amount of aldehyde **12**. The mixture was dissolved in 3% aqueous $HClO_4$ and tetrahydrofuran (1:1) and the reaction was stirred at 0 °C for 1 h and at room temperature for 3 h. The solution was extracted into methylene chloride (2x). The organic layer was washed with $NaHCO_3$ (2x) and NaCl (1x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure to yield 1.14 g (4.53 mmol, 94%) of **12**, which was used without further purification: IR 2830, 2720, 1737, 1527, 1353 cm^{-1}; ^1H NMR δ 9.76 (s, 1 H), 7.91 (d, J = 8.1 Hz, 1 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.59-7.42 (complex, 2 H), 4.21 (t, J = 6.9 Hz, 1 H), 3.67 (s, 3 H), 2.65-2.45 (complex, 3 H), 2.20 (m, 1 H); ^{13}C NMR δ 200.8, 172.5, 149.3, 133.3, 132.9, 129.9, 128.5, 124.9, 52.4, 45.3, 41.7, 25.1; HRMS *m/z*: Calcd for $C_{12}H_{13}NO_5$: 251.0793; Found: 251.0791.

Representative Procedure for Reduction-Reductive Amination: Methyl (±)-(2*R,5*S**)-2-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (13).** To a solution of 1.00 g (3.77 mmol) of **6** in 200 mL of methanol was added 200 mg of 5% palladium-on-carbon. The mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atm of hydrogen for 3 h at 30 °C. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite topped with a layer of $MgSO_4$ to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by PTLC using increasing concentrations of ether in hexanes (5-50%). Band 2 (from the top) gave 740 mg (3.38 mmol, 90%) of **13** as a light yellow oil that crystallized upon standing, mp 102-104 °C. IR 3359, 1737 cm^{-1}; ^1H NMR δ

7.11 (t, J = 7.6 Hz, 1 H), 7.04 (d, J = 7.6 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 6.75 (d, J = 7.7 Hz, 1 H), 3.85 (dd, J = 8.3, 2.7 Hz, 1 H), 3.66 (s, 3 H), 2.91 (m, 1 H), 2.41 (m, 1 H), 1.78-1.64 (complex, 3 H), 1.22 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 173.7, 148.6, 131.2, 130.4, 127.9, 121.2, 120.8, 53.6, 51.8, 50.3, 34.9, 28.1, 24.0; HRMS *m/z*: Calcd for $C_{13}H_{17}NO_2$: 219.1259; Found: 219.1258.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.84; N, 6.42.

Methyl (±)-(2*S, 5*S**)-2-Methyl-2,3,4,5-tetrahydro -1*H* -1-benzazepine-5-carboxylate (14).** Band 1: 70 mg (0.32 mmol, 9%); mp 45-47 °C; IR 3353, 1730 cm^{-1}; ^{1}H NMR δ 7.07 (t, J = 7.5 Hz, 1 H), 6.94 (d, J = 7.6 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 6.73 (d, J = 7.6 Hz, 1 H), 3.84 (dd, J = 8.5, 2.0 Hz, 1 H), 3.75 (s, 3H), 3.05 (m, 1 H), 2.19 (m, 1 H), 1.94-1.81 (complex, 2 H), 1.58-1.45 (complex, 1 H), 1.20 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 175.3, 148.3, 129.7, 128.8, 127.4, 121.0, 120.3, 52.5, 51.8, 48.9, 36.2, 27.5, 23.3; HRMS *m/z*: Calcd for $C_{13}H_{17}NO_2$: 219.2828; Found: 219.2825.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.82; N, 6.42.

Reduction-Reductive Amination of Methyl (±)-2-(2-Nitrophenyl)-5-oxoheptanoate (7): Methyl (±) - (2*R, 5*S**)-2-Ethyl- 2, 3, 4, 5-tetrahydro -1*H* -1-benzazepine-5-carboxylate (15).** Band 2: 540 mg (2.32 mmol, 65%); mp 74-76 °C; IR 3360, 1728 cm^{-1}; ^{1}H NMR δ 7.11 (t, J = 7.6 Hz, 1 H), 7.03 (d, J = 7.5 Hz, 1 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 3.85 (dd, J = 6.2, 2.5 Hz, 1 H), 3.66 (s, 3 H), 2.66 (m, 1 H), 2.43 (m, 1 H), 1.78-1.63 (complex, 3 H), 1.52 (quintet, J = 7.3 Hz, 2 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 173.8, 148.6, 130.9, 130.5, 127.9, 121.2, 120.8,

59.7, 51.8, 50.2, 32.7, 30.1, 28.0, 10.8; HRMS *m/z*: Calcd for $C_{14}H_{19}NO_2$: 233.1416; Found: 233.1414.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.27; H, 8.26; N, 5.93.

Methyl (±)-(2*S, 5*S**)-2-Ethyl- 2, 3, 4, 5-tetrahydro -1*H*-1-benzazepine-5-carboxylate (16).** Band 1: 70 mg (0.30 mmol, 8%); mp 46-48 °C; IR 3365, 1735 cm^{-1}; ^1H NMR δ 7.07 (t, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.85 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 3.85 (dd, *J* = 8.4, 2.3 Hz, 1 H), 3.74 (s, 3 H), 2.81 (m, 1 H), 2.15 (m, 1 H), 1.99-1.84 (complex, 3 H), 2.81 (m, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR δ 175.2, 148.2, 129.5, 129.1, 127.4, 120.8, 120.3, 58.3, 51.9, 49.0, 33.5, 29.5, 27.0; HRMS *m/z*: Calcd for $C_{14}H_{19}NO_2$: 233.1416; Found: 233.1413.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.25; N, 5.89.

Reduction-Reductive Amination of Methyl (±)-2-(2-Nitrophenyl)-5-oxo-5-phenylpentanoate (8): (±)-3-(3-Phenylpropyl)-2-indolinone (17). Band 3: 120 mg (0.48 mmol, 31%); mp 82-83 °C (lit. mp 84-85 °C)[40]; IR 3321, 1711, 1631, 1473 cm^{-1}; ^1H NMR δ 7.66 (s, 1 H), 7.28-7.12 (complex, 7 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 3.49 (t, *J* = 6.0 Hz, 1 H), 2.64 (m, 2 H), 2.01 (m, 2 H), 1.79-1.60 (complex, 2 H); ^{13}C NMR δ 180.7, 141.8, 141.6, 129.6, 128.3, 128.2, 127.8, 125.8, 124.0, 122.2, 109.8, 46.0, 35.8, 30.1, 27.5; HRMS *m/z*: Calcd for $C_{17}H_{17}NO$: 251.1310; Found: 251.1307.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.06; H, 6.77; N, 5.74.

Methyl (±)-(2*R, 5*S**)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (18).** Band 2: 70 mg (0.25 mmol, 16%); mp 82-84 °C; IR 3344, 1739 cm^{-1}; ^1H NMR δ 7.41-7.62 (complex, 5 H), 7.10 (t, J = 7.5 Hz, 1 H), 6.99 (d, J = 7.4 Hz, 1 H), 6.92 (t, J = 7.4 Hz, 1 H), 6.75 (d, J = 7.9 Hz, 1 H), 3.99-3.92 (complex, 2 H), 3.78 (s, 3 H), 2.22 (m, 1 H), 2.25-1.89 (complex, 3 H); ^{13}C NMR δ 175.4, 148.0, 145.4, 130.6, 128.8, 128.0, 127.5, 127.4, 126.4, 121.6, 120.8, 62.3, 51.8, 48.6, 36.9, 27.8; HRMS *m/z*: Calcd for $C_{18}H_{19}NO_2$: 281.1416; Found: 281.1414.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.71; H, 6.74; N, 5.09.

Methyl (±)-(2*S, 5*S**)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (19).** Band 1: 10 mg (0.04 mmol, 3%); mp 68-70 °C; IR 3349, 1733 cm^{-1}; ^1H NMR δ 7.39-7.26 (complex, 5 H), 7.15-7.10 (complex, 2 H), 6.93 (t, J = 7.3 Hz, 1 H), 6.75 (d, J = 7.6 Hz, 1 H), 3.94 (dd, J = 5.9, 3.4 Hz, 1 H), 3.85 (dd, J = 11.2, 1.9 Hz, 1 H), 3.70 (s, 3 H), 2.52 (m, 1 H), 2.15 (m, 1 H), 1.97-1.65 (complex, 2 H); ^{13}C NMR δ 173.5, 148.4, 145.7, 131.3, 130.4, 128.7, 128.1, 127.5, 126.4, 121.6, 121.0, 63.4, 51.9, 50.1, 35.2, 28.1; HRMS *m/z*: Calcd for $C_{18}H_{19}NO_2$: 281.1416; Found: 281.1415.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.79; H, 6.83; N, 5.02.

Catalytic Hydrogenation of Dimethyl (±)-2-(2-Nitrophenyl)pentanedioate (9): Dimethyl (±)-2-(2-Aminophenyl)pentanedioate (20). 650 mg (2.59 mmol, 97%); IR 3411, 1744, 1732 cm^{-1}; ^1H NMR δ 7.10-7.04 (complex, 2 H), 6.80-6.68 (complex, 2 H), 3.78 (t, J = 7.4 Hz, 1 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.41-2.32 (complex, 3 H), 2.15

(m, 1 H); ^{13}C NMR δ 174.0, 173.9, 144.9, 128.2, 127.9, 122.7, 118.9, 116.7, 52.2, 51.7, 45.4, 31.4, 25.8; HRMS *m/z*: Calcd for $C_{13}H_{17}NO_4$: 251.1157; Found: 251.1155.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found; C, 61.97; H, 6.75; N, 5.66.

Methyl (±)-3-(2-Oxoindolin-3-yl)propanoate (21). A solution of 650 mg (2.59 mmol) of **20** was dissolved in benzene and heated at 50 °C. The reaction progress was monitored by TLC. After 5 days, the solution was concentrated under reduced pressure and purified by PTLC using 50% ether in hexanes. The major band afforded 430 mg (1.96 mmol, 76%) of **21** as a light yellow oil that crystallized upon standing; mp 69-72 °C. IR 3259, 1733, 1711 cm^{-1}; ^{1}H NMR δ 9.11 (s, 1 H), 7.28-7.22 (complex, 2 H), 7.03 (t, J = 7.5 Hz, 1 H), 6.92 (d, J = 7.6 Hz, 1 H), 3.63 (s, 3 H), 3.55 (t, J = 5.9 Hz, 1 H), 2.57-2.21 (complex, 4 H); ^{13}C NMR δ 180.1, 173.3, 141.6, 128.6, 128.1, 124.1, 122.4, 109.9, 51.6, 44.9, 30.0, 25.4; HRMS *m/z*: Calcd for $C_{12}H_{13}NO_3$: 219.0895; Found: 219.0892.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 6.01; N, 6.45.

Reduction-Reductive Amination of Methyl (±)-2-(2-Nitrophenyl)-5-oxopentanoate (12): Methyl (±)-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (22). 280 mg (1.37 mmol, 60 %); IR 3366, 1730 cm^{-1}; ^{1}H NMR δ 7.10 (t, J = 7.6 Hz, 1 H), 7.01 (d, J = 7.6 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 6.75 (d, J = 7.7 Hz, 1 H), 3.86 (dd, J = 7.3, 2.1 Hz, 1 H), 3.70 (s, 3 H), 3.13 (m, 1 H), 3.00 (m, 1 H), 2.20 (m, 1 H), 1.93-1.76 (complex, 3 H); ^{13}C NMR δ 174.4, 149.9, 130.4, 130.1, 127.7, 121.0, 120.2, 51.8, 50.2, 48.0, 28.5, 28.1; HRMS *m/z*: Calcd for $C_{12}H_{15}NO_2$: 205.1103; Found: 205.1101.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.39; H, 7.42; N, 6.75.

Acknowledgements. Support of this work by the NIH (GM54256) and by the Oklahoma Center for the Advancement of Science and Technology (HR01-015) was greatly appreciated. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

CHAPTER IV

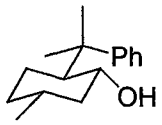
CHIRAL 2-ALKYL- 2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINES BY A TANDEM REDUCTION-REDUCTIVE AMINATION

Introduction

The chirality present in biological systems has made the synthesis of enantiomerically pure compounds essential. An approach to controlling the stereochemistry in the preparation of chiral compounds is asymmetric synthesis. Asymmetric synthesis involves the transformation of a prochiral molecule into a chiral product. This can be accomplished by the temporary introduction of an auxiliary group (called a chiral auxiliary) containing one or more stereocenters which directs the introduction of chirality into the prochiral molecule through a diastereoselective transformation. This process is termed asymmetric induction. Subsequent removal of the chiral auxiliary produces a compound containing a newly formed stereocenter with high enantiomeric purity. Chiral auxiliaries that are inexpensive or recyclable are ideal in this type of asymmetric synthesis.[41]

Chiral auxiliaries derived from menthol were introduced by Corey[42] in 1975 and have been used in a large number of diastereoselective syntheses since that time. One of the most useful menthol derivatives used as a chiral auxiliary is (-)-8-phenylmenthol (**1**) (Figure 40). This chiral auxiliary can influence the diastereoselectivity of a reaction to

produce compounds with >90% *de*.[43] Control of the stereochemistry at the position β to the attachment of the 8-phenylmenthol chiral auxiliary is the most effective, since this position is closest to the phenyl group present on the auxiliary.



1

Figure 40. (-)-8-phenylmenthol.

Bunce and co-workers have described a tandem reduction-reductive amination sequence for the diastereoselective synthesis of 2-alkyl-tetrahydroquinoline-4-carboxylate esters. This method has recently been extended to the synthesis of enantiomerically pure 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylate esters through the use of the (-)-8-phenylmenthol chiral auxiliary esterified to the substrate. In the present work, the conjugate addition of (-)-8-phenylmenthyl ester enolates to α,β-unsaturated ketones occurred with moderate diastereoselectivity. This chapter will discuss the ability of the chiral auxiliary to stereodifferentiate the faces of (-)-8-phenylmenthyl ester enolates in alkylation reactions. Application of this method to the enantioselective synthesis of 2-alkyl-1*H*-1-benzazepine-5-carboxylate esters using (-)-8-phenylmenthol will also be described.

Alkylations with Alkyl Halides. The alkylation of (-)-8-phenylmenthyl phenylacetate (**2**) was demonstrated by Solladié-Cavallo and co-workers[44] to be diastereoselective (Figure 41). Esterification of phenylacetic acid with (-)-8-phenylmenthol (**1**) using DCC (1,3-dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine) in ether produced (-)-8-phenylmenthyl phenylacetate (**2**) in 95%

yield. Treatment of **2** with LDA in tetrahydrofuran at –50 °C followed by reaction with methyl iodide produced **3** and **4** with 98% overall yield, but with no diastereoselectivity (diastereomeric ratio 1:1). Alkylations with larger alkyl halides improved the diastereoselectivity. For example, alkylation of **2** with benzyl bromide using butyllithium in tetrahydrofuran gave **5** and **6** in 93% overall yield and with a diastereomeric ratio of 69:31.

The addition of DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone] increased the diastereoselectivity of the alkylation with methyl iodide to 4:1 in 90% overall yield. The improvement of diastereoselectivity by the addition of DMPU was explained to be due to a decrease in the level of aggregation between enolates and the metal cation. Aggregation occurs at the side of the enolate not hindered by the chiral auxiliary. This prevents alkylation at the less hindered side, thus the diastereoselective action of the chiral auxiliary is diminished. This argument was reinforced by the use of the Schwesinger (*t*-BuP4) base. The *t*-BuP4 base is known to generate a nonaggregated enolate.[45] Alkylation of (-)-8-phenylmenthyl phenylacetate (**2**) with ethyl iodide using *t*-BuP4 base yielded **7** and **8** in 95% overall yield with a high degree of diastereoselectivity (>98:2). Removal of the chiral auxiliary was accomplished by reduction of ester **7** with lithium aluminum hydride in tetrahydrofuran to yield (-)-8-phenylmenthol (**1**) and chiral alcohol **9** in 90% yield.

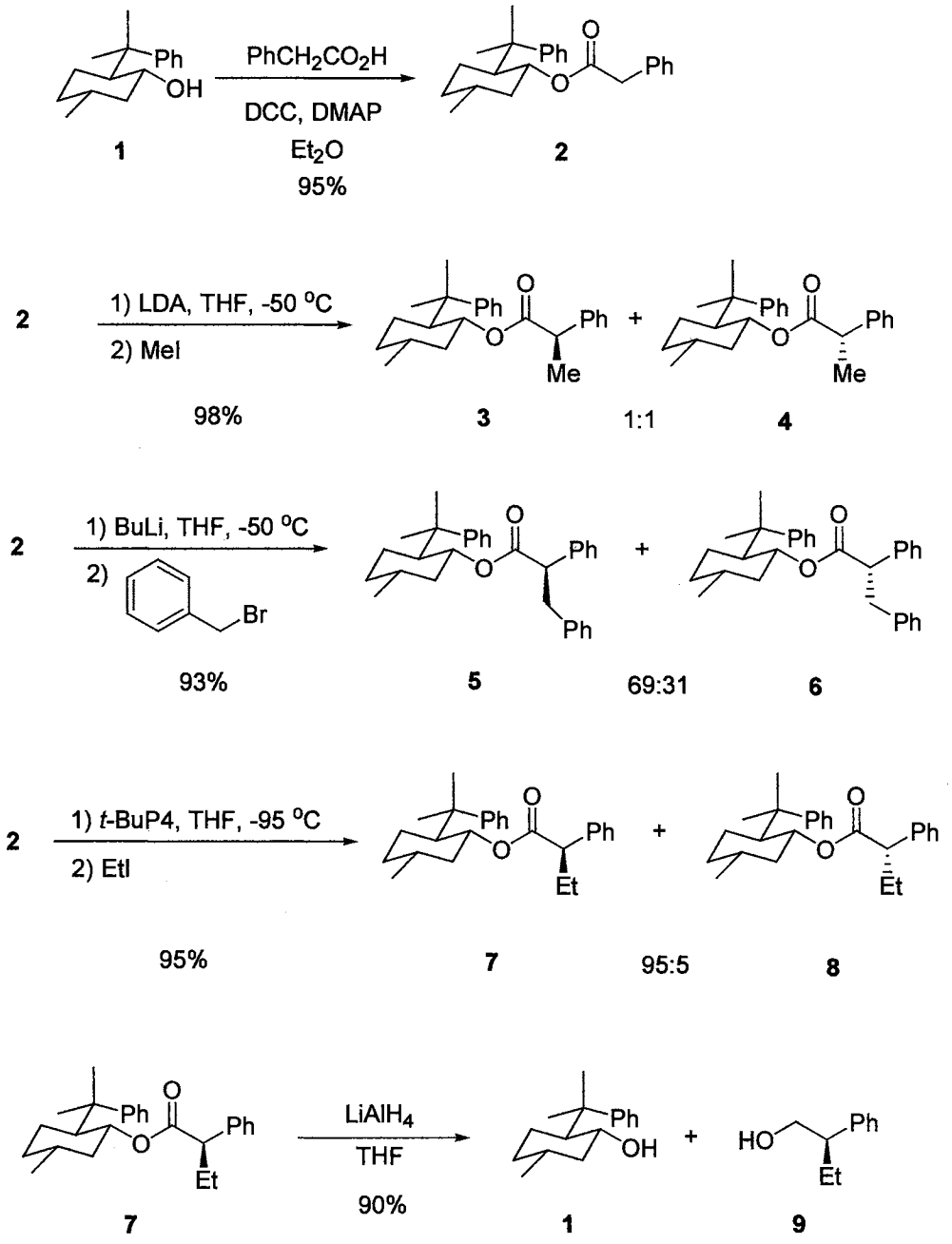


Figure 41. Alkylation of (-)-8-phenylmenthyl phenylacetate (**2**) with various alkyl halides, and cleavage of the chiral auxiliary.

Fukomoto and co-workers[46] used a diastereoselective alkylation of (-)-8-phenylmenthyl hydrogen malonate (**10**) in a synthesis of α-alkyl-α-amino acids. Treatment of **10** with two equivalents of LDA followed by reaction with ethyl iodide

produced **11** and **12** in 83% overall yield and a diastereomeric ratio of 4:1. Alkylation of **10** with benzyl bromide under the same conditions gave **13** and **14** in 72% overall yield and a diastereomeric ratio of 12:1 (Figure 42).

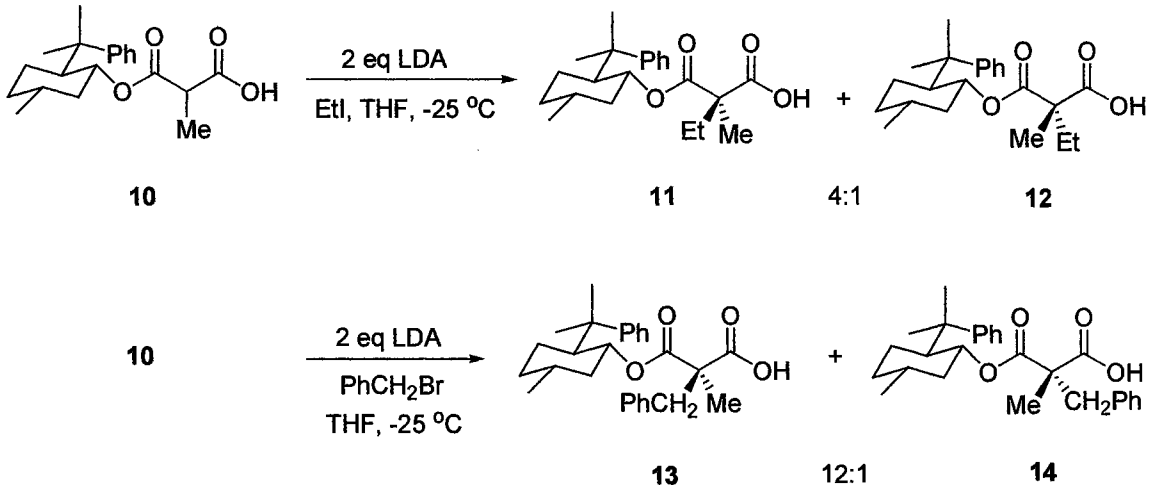


Figure 42. Diastereoselective alkylation of (-)-8-phenylmenthyl hydrogen malonate **10** with ethyl iodide and benzyl bromide.

Nouguier and co-workers[47] investigated the effectiveness of various chiral auxiliaries on the alkylation of esters of 2-nitropropanoic acid with *p*-nitrobenzyl chloride (Figure 43). The (-)-8-phenylmenthyl ester of 2-nitropropionic acid **15** was alkylated with *p*-nitrobenzyl chloride in DMF (dimethylformamide) containing sodium hydride at room temperature. Alkylation of **15** gave **16** in 22% overall yield with a 60% *de*.

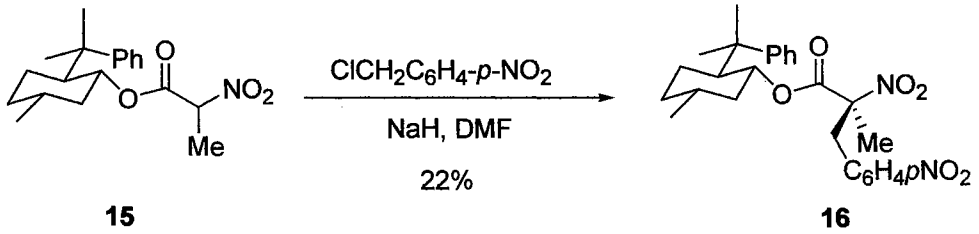


Figure 43. Diastereoselective alkylation of 2-nitropropionate ester **15**.

Conjugate Additions. Corey and Peterson[48] investigated the diastereoselective Michael addition of enolates derived from (-)-8-phenylmenthol with crotonates (Figure 44). Reaction of (-)-8-phenylmenthol (**1**) with propanoyl chloride in benzene containing pyridine gave ester **17**. Ester **17** was converted to *Z*-enolate **18** by treatment with LDA in tetrahydrofuran at −78 °C.[49] Reaction of **3** with methyl (E)-2-butenoate produced two sets of products, the predominate products being threo (the methyl substituents are on opposite sides of a Newman projection of the molecule when the ester groups are eclipsed), **19** and **20** in 90% overall yield. The diastereomeric ratio of **19** to **20** was 95:5.

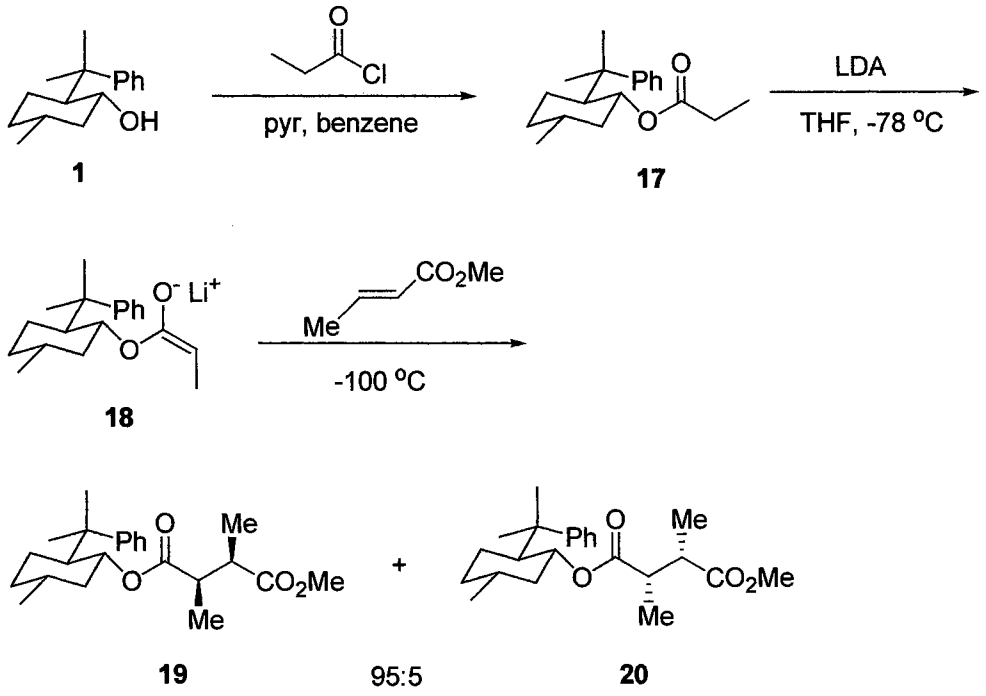


Figure 44. Michael addition of *Z*-enolate to methyl (E)-2-butenoate.

The preference for the threo products was rationalized by investigation of the mechanism of attack by the *Z*-enolate with methyl (E)-2-butenoate (Figure 45). The enolate oxygen, the ester carbonyl, and the methoxy oxygen all coordinate the lithium

counterion as the substrates approach each other and in the transition state. This conformation leads to the threo stereochemistry between the two methyl groups in the product. The diastereomeric ratio of 95:5 between the two threo diastereomers arises from the (-)-8-phenylmenthyl chiral auxiliary blocking the attack of methyl (E)-2-butenoate at the backside of the enolate.

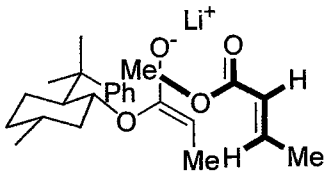


Figure 45. Coordination of the ester enolate and methyl (E)-2-butenoate to the lithium counterion.

The reaction of indole-containing enolates with *N*-alkyl-3-vinylpyridinium salts has been used in the synthesis mavacurine type alkaloids.[50] Mavacurine type alkaloids are tryptophan containing compounds derived from plants of the genus *Strychonos*. Several of the mavacurine alkaloids are being studied for use as muscle relaxants.[21] Bennasar and co-workers[51] attempted a stereoselective synthesis of C-mavacurine alkaloids using (-)-8-phenylmenthyl esters (Figure 46). The reaction of indole (**27**) and chloroacetate **28** using sodium hydride in DMF at 0 °C gave (-)-8-phenylmenthyl ester **29** in 78% yield. (-)-8-Phenylmenthyl ester **29** was treated with LHMDS (lithium hexamethyldisilazide) in tetrahydrofuran at –78 °C and reacted with pyridinium iodide **30**. The temperature was increased to –30 °C and a dry solution of HCl in benzene was added to give a mixture of diastereomers **31** and **32** in 28% overall yield. The diastereomeric ratio of **31** to **32** was 2.5:1. The use of LDA as the base did not improve the diastereoselectivity.

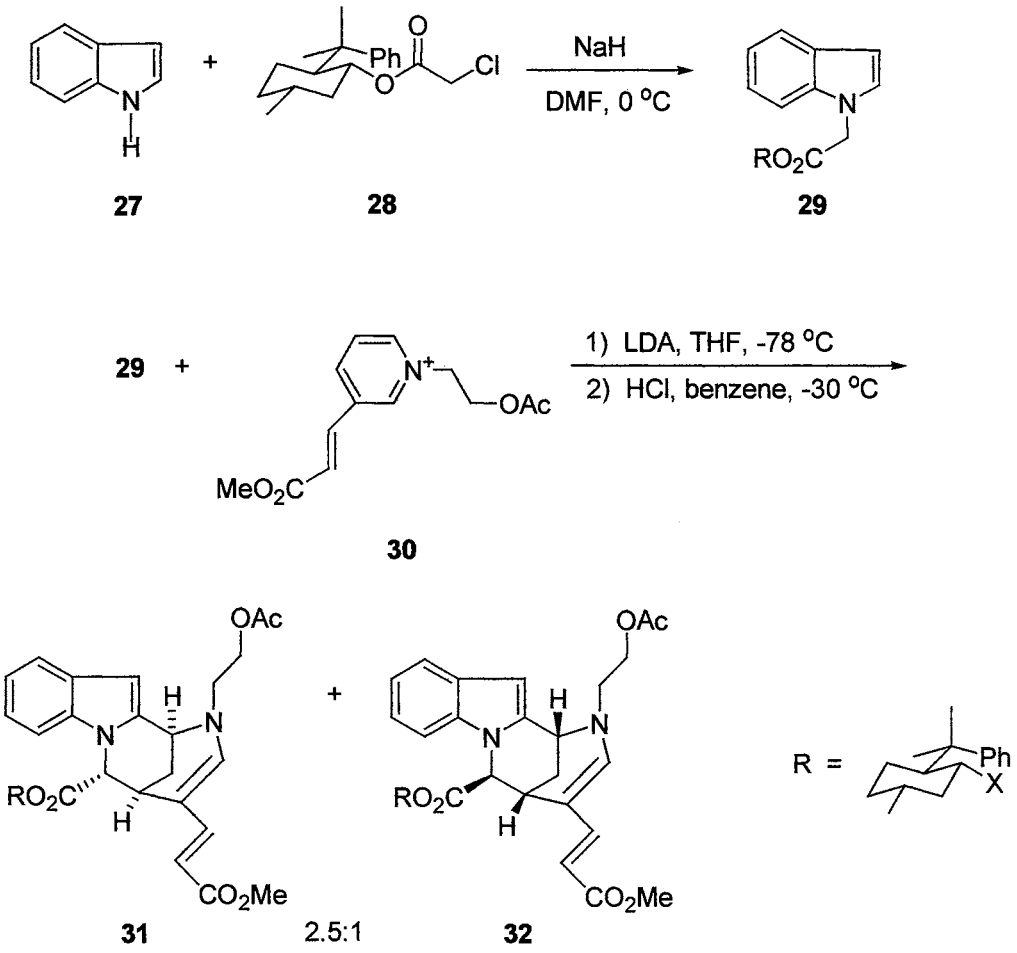


Figure 46. Attempted enantioselective synthesis of C-mavacurine alkaloids **31** and **32**.

The ratio of diastereomers **31** to **32** was rationalized by considering the reaction mechanism. The enolate of **29** attacks the para position of the pyridinium ion **30**, forming intermediate **33**. Intermediate **33** is then protonated forming intermediate **34** which undergoes a regiospecific cyclization resulting in formation of the products **31** and **32**, which display a cis relationship between the bridgehead hydrogens on C3 and C15 (Figure 47). Both **31** and **32** have a trans relationship between the hydrogens on C15 and C16, which was shown by previous studies to occur with a diastereoselectivity of 5:1.[51]

The 2.5:1 ratio between products **31** and **32** therefore arises from the reaction of the enolate of **29** with pyridinium iodide **30**.

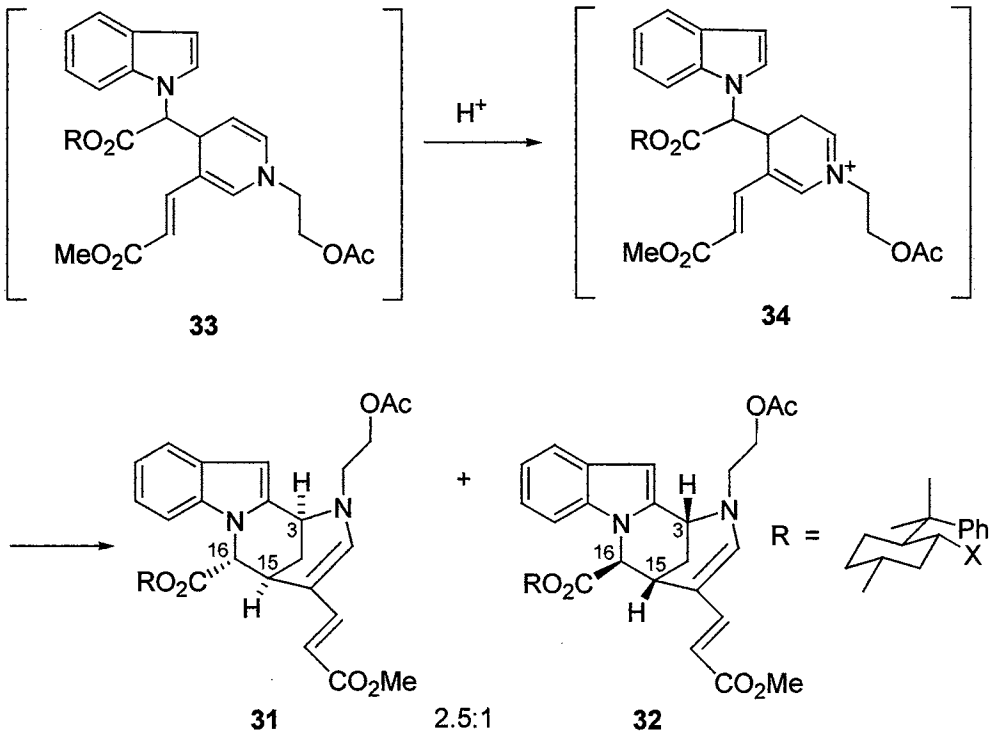


Figure 47. Intermediates in the regiospecific cyclization leading to C-mavacurine alkaloids **31** and **32**.

RESULTS

Synthesis of (-)-8-Phenylmenthol. The procedure reported by Ort[52] for the synthesis of (-)-8-phenylmenthol was followed. Commercially available technical grade (*R*)-(+)-pulegone (**35**) was reacted with phenylmagnesium bromide in the presence of copper(I) bromide to give the 1,4-addition products **36** and **37**. Equilibration of the product mixture using potassium hydroxide in 90% ethanol produced an 87:13 mixture of **36** and **37,** respectively, in 78% overall yield (Figure 48).

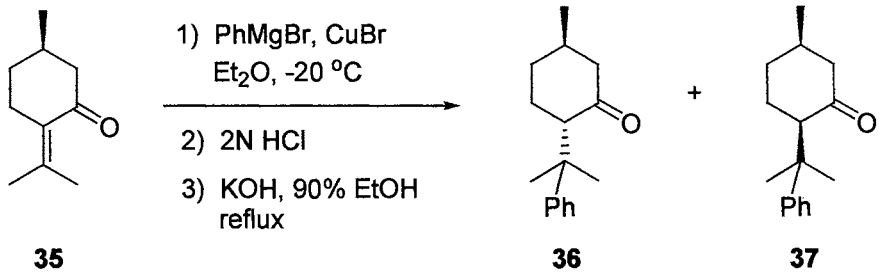


Figure 48. 1,4-Addition of phenylmagnesium bromide to (*R*)-(+)-pulegone.

The equilibrated mixture of ketones **36** and **37** was reduced using metallic sodium and isopropyl alcohol in toluene at reflux to produce alcohols **38** and **39** in 85% overall yield. Reaction of the alcohols with chloroacetyl chloride in methylene chloride at 0 °C containing DMAP and TEA (triethylamine) followed by fractional crystallization of the diastereomeric chloroacetates produced pure **40** in 44% yield from the mixture of alcohols (Figure 49).

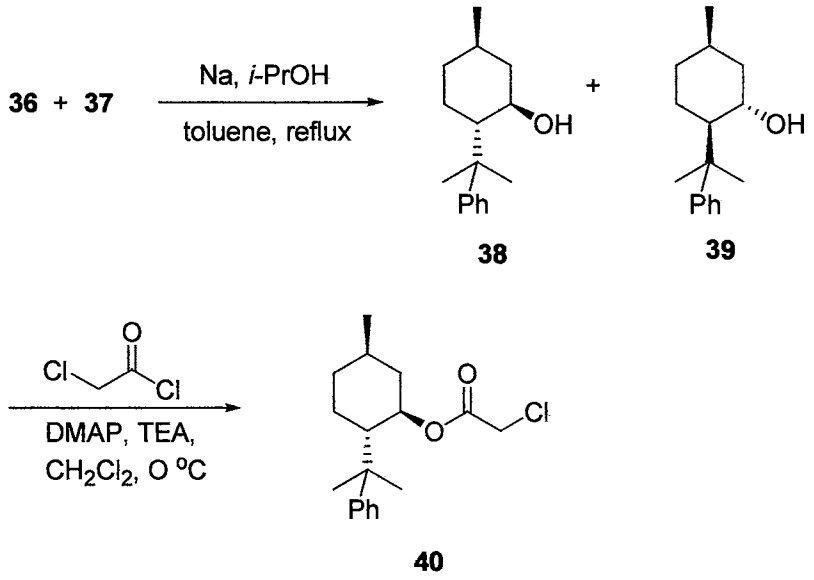


Figure 49. Synthesis of chloroacetate diastereomer of (-)-8-phenylmenthol.

Ester **40** was purified by kinetic crystallization from anhydrous ethanol. Hydrolysis of ester **40** by treatment with potassium hydroxide in 90% ethanol followed by vacuum distillation produced optically pure **1**. The optical rotation of **1** was $[\alpha]_D^{23}$ = -26° (lit value $[\alpha]_D^{23}$ = -26.4°),[52] demonstrating that the product had been isolated with >95% optical purity. The reaction producing pure (-)-8-phenylmenthol (**1**) is shown in Figure 50.

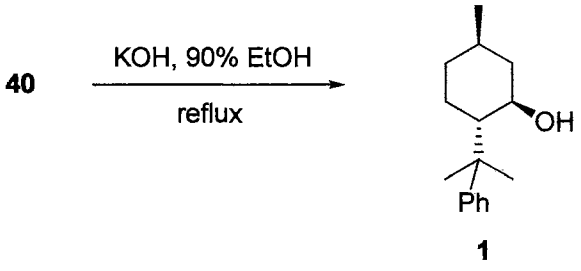


Figure 50. Hydrolysis of chloroacetate ester **40** to produce (-)-8-phenylmenthol.

Synthesis of (-)-8-phenylmenthyl ester of 2-nitrophenylacetic acid. Reaction of 2-nitrophenylacetic acid (**41**) with thionyl chloride produced acid chloride **42**. Following removal of the excess thionyl chloride, **42** was esterified at 0 °C with alcohol **1** in methylene chloride containing DMAP and TEA to produce optically pure ester **43** in 76% yield from the alcohol (Figure 51).

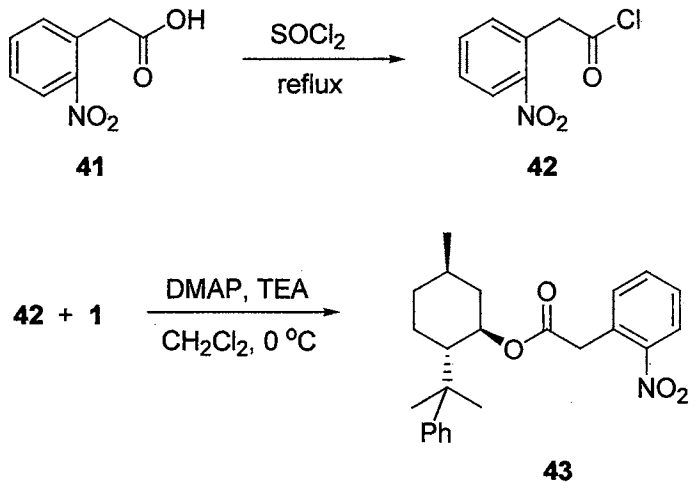


Figure 51. Synthesis of 2-nitrophenylacetyl ester of (-)-8-phenylmenthol.

Diastereoselective Synthesis of Cyclization Substrates. The conjugate addition reactions of (-)-8-phenylmenthyl ester **43** with vinyl ketones **44-45** are shown in Figure 52. The reactions were carried out in dry acetonitrile containing 8.4 equivalents of potassium carbonate and a catalytic amount of 18-crown-6.[34] The reaction was set up at 0 °C and gradually warmed to 20 °C over 12 hours producing ketones **46-49**. The overall yields of the alkylations were 64% (for products **46** and **47**) and 58% (for products **48** and **49**). In both cases, the alkylations yielded diastereomeric mixtures that could not be separated chromatographically. The diastereomeric ratios, determined by ^{1}H NMR, were 5:1 (for products **46** and **47**) and 3:1 (for products **48** and **49**).

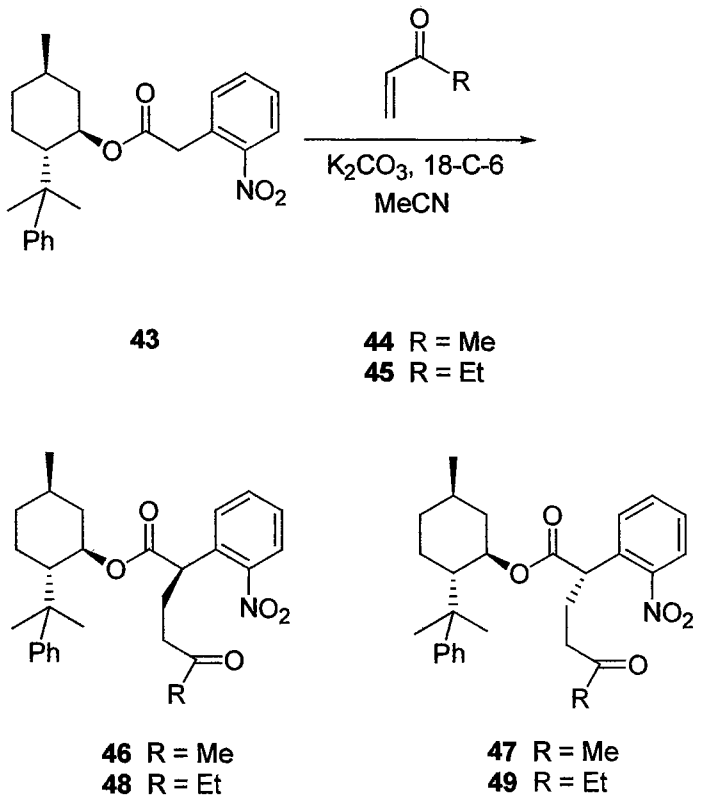
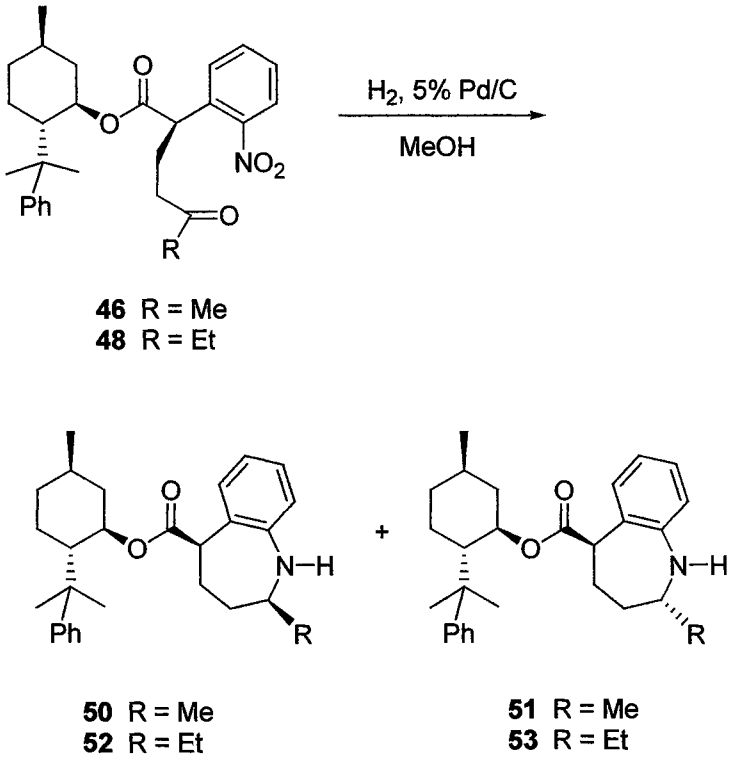


Figure 52. Alkylation of 2-nitrophenylacetyl ester of (-)-8-phenylmenthol with substituted vinyl ketones.

Synthesis of Chiral 2,5-Disubstituted 2,3,4,5-Tetrahydro-1*H*-1-Benzazepines. The reduction-reductive amination of compounds **46/47** and **48/49** is illustrated in Figure 53. The reduction of **46/47** and **48/49** in methanol under 4 atm of hydrogen using 5% palladium-on-carbon catalyst gave products **50-53** in overall yields of 52% for methyl-substituted products **50** and **51** and 70% for ethyl-substituted products **52** and **53**. For the methyl-substituted products **50** and **51**, the cis:trans ratio was 13:1; the cis:trans ratio for the ethyl-substituted products **52** and **53** was 7:1. The reduction-reductive amination products were also isolated as mixtures of diastereomers as a result of the moderate diastereoselectivity of the conjugate addition of **43** with **44** and **45**. The diastereomeric

mixtures could not be separated chromatographically, and ^{1}H NMR data showed that the minor diastereomers were present in ratios similar to those observed with the conjugate addition products.



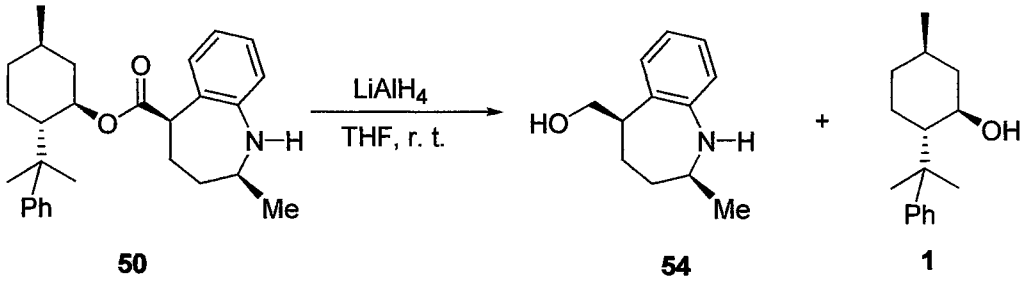
46 R = Me
48 R = Et

50 R = Me
52 R = Et

51 R = Me
53 R = Et

Figure 53. Tandem reduction-reductive amination of nitro ketones **46** and **47**.

Removal of the Chiral Auxiliary. To demonstrate that the chiral auxiliary could be recycled and that the optical activity of the (-)-8-phenylmenthol had been retained, ester **50** was reduced with lithium aluminum hydride in tetrahydrofuran[53] to give alcohols **54** and **1** in 55% yield (Figure 54). The recovered (-)-8-phenylmenthol displayed essentially the same optical rotation as the starting material ($[\alpha]_D^{23}$ = -26°, lit value $[\alpha]_D^{23}$ = -26.4°).



50 **54** **1**

Figure 54. Removal of the (-)-8-phenylmenthol chiral auxiliary.

Discussion. The conjugate addition of (-)-8-phenylmenthyl ester **43** to vinyl ketones **44** and **45** occurred with moderate diastereoselectivity to give products **46** and **47** with a diastereomeric ratio of 5:1 and products **48** and **49** with a diastereomeric ratio of 3:1. A factor contributing to moderate diastereoselectivity may be the reaction temperature. The reaction progress was monitored by TLC, which indicated that the reaction proceeded only at temperatures near 20 °C. Higher reaction temperatures have been demonstrated to reduce the diastereoselective action of the (-)-8-phenylmenthol chiral auxiliary.[54] Another factor contributing to the moderate diastereoselectivity is the reversibility of the conjugate addition. Enolization of the initial addition product and reversion back to the starting materials may contribute to the formation of the minor diastereomers.[55]

As demonstrated previously for the synthesis of the 2,5-disubstituted 2,3,4,5-tetrahydro-1*H*-1-benzazepine products, the major product in the chiral series has the cis orientation of groups at C2 and C5. The diastereoselectivity of the reduction-reductive amination arises from the addition of a hydrogen molecule to the final imine intermediate cross the face opposite the ester (Figure 38). The diastereoselective ratios for the methyl

(**50** and **51**) and ethyl products (**52** and **53**) were 13:1 and 7:1, respectively, compared with 11:1 and 8:1 for methyl ester products.

Removal of the chiral auxiliary was accomplished by reduction of (-)-8-phenylmenthyl ester **50** using lithium aluminum hydride to give alcohol **54** and pure (-)-8-phenylmenthol (**1**) in 55% yield. The isolation of pure (-)-8-phenylmenthol demonstrated that the chiral auxiliary could be recycled and that it had the same optical rotation as the starting material.

Conclusion. This work represents an attempt to extend the previous enantioselective synthesis of pure 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylate esters to 2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters. The key step in the synthesis is the diastereoselective conjugate addition of (-)-8-phenylmenthyl 2-nitrophenyl acetate to α,β-unsaturated ketones. The diastereoselectivities of the alkylations were moderate, resulting from the higher reaction temperature requirement and the inherent reversibility of the conjugate additions. Subsequent reduction-reductive amination of the nitroketones produced 2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic ester products with a high degree of diastereoselectivity. The recovery of optically pure (-)-8-phenylmenthol demonstrates that the chiral auxiliary can be recycled.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Potassium carbonate was ground to a fine powder, dried under vacuum for 24 h at 120 °C, and stored in an oven at 120 °C until needed. Magnesium turnings were kept in an oven at 120 °C and ground in a mortar and pestel prior to use. The copper(I) bromide was purified by dissolving in a 2 M HBr solution followed precipitation by dilution with water and vacuum filtration. The filter cake was washed with anhydrous ethanol and ether then dried and stored at 0 °C.[56] All reactions were run under dry nitrogen and in oven-dried glassware. The HCl (0.2 M, 1 M, 2 M, and 6 M), NaOH (0.2 M and 1 M), $NaHCO_3$ (saturated), and NaCl (saturated) used in various procedures were aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on silica gel GF plates (Analtech no. 21521) with UV detection, or (2) capillary GC (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50-300°C. Preparative separations were performed by one of the following methods: (1) flash column chromatography on silica gel (grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies UV- 5) or (2) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Band elution for both methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were were run as thin films on NaCl disks and referenced to polystyrene. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using $(CH_3)_4Si$ as an internal standard. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

(2*RS*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone (36, 37). In a 500-mL, three-necked, round-bottomed flask fitted with a reflux condenser carrying a

$CaCl_2$ drying tube, a magnetic stir bar, and a 250-mL addition funnel was placed 5.40 g (0.23 mol) of magnesium turnings and 25 mL of ether. To this flask was added 3.92 g (25.0 mmol) of bromobenzene in 25 mL of ether and the flask was warmed to initiate formation of the Grignard reagent. After the reaction had started, 35.3 g (0.22 mol) of bromobenzene in 150 mL of ether was added dropwise over 1 h. After the addition of bromobenzene was complete, the reaction was heated to reflux for 1 h. The solution was cooled to room temperature, and an additional 200 mL of ether was added to give a total volume of about 400 mL. A nitrogen inlet and a pierced rubber septum with a stainless steel tube inlet replaced the reflux condenser and pressure-equalizing funnel, respectively.

In a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser carrying a $CaCl_2$ drying tube, and a rubber septum was added 2.25 g (15.6 mmol) of copper(I) bromide and 100 mL of ether. The mixture was vigorously stirred and cooled to –20 °C. The ethereal Grignard solution from the first reaction flask was transferred to the second flask through the stainless steel cannula using nitrogen pressure. After addition of the Grignard solution, the rubber septum was replaced by a 250-mL addition funnel containing 21.6 g (0.14 mol) of (*R*)-(+)-pulegone (**35**) in 100 mL of ether. This solution was added with stirring to the dark-green reaction mixture over 2 h. After the addition was complete, the reaction mixture was stirred overnight at –5 °C. To the vigorously stirred reaction mixture was added 150 mL of an ice-cold solution of 2 M HCl. The organic layer was separated and filtered with suction, and the residue on the funnel was washed with an additional 50 mL of ether. The aqueous layer was saturated with NH_4Cl (aq) and extracted with 100 mL of ether (3x).

The combined organic layers were washed with $NaHCO_3$ (2x) and NaCl, dried ($MgSO_4$), and vacuum filtered to remove solids. The solvent was evaporated under reduced pressure to give 24.3 g (0.11 mol, 75%) of the crude products **36** and **37** that were used without further purification.

The crude mixture of **36** and **37** was dissolved in 350 mL of 90% ethanol. To this solution was added 35.0 g (0.63 mol) of potassium hydroxide pellets. The solution was stirred at reflux for 8 h. After cooling to room temperature, the solution was concentrated under reduced pressure to a volume of approximately 50 mL followed by the addition of 200 mL of water. The solution was saturated with NaCl and extracted with 50 mL of ether (4x). The combined organic layers were dried ($MgSO_4$), vacuum filtered to remove solids, and concentrated under reduced pressure. Vacuum distillation gave three fractions: the first fraction (boiling range <80 °C) was discarded. The second fraction (boiling range 80-100 °C, 0.05 mm Hg) consisted mainly of biphenyl. The third fraction (boiling range 100-110 °C, 0.05 mm Hg) yielded 23.7 g (103 mmol, 74%) of equilibrated ketones **36** and **37** (87:13).

(1*RS*,2*SR*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (38, 39). In a 250-mL, three-necked, round-bottomed flask fitted with a reflux condenser carrying a $CaCl_2$ tube, a mechanical stirrer, and a 125 mL addition funnel was placed 6.60 g (288 mmol) of metallic sodium in 90 mL of toluene. The mixture was stirred vigorously and heated to reflux. Once a fine suspension of sodium was obtained, a solution of 22.7 g (98.5 mmol) of equilibrated **36** and **37** in 16.3 g (20.7 mL, 276 mmol) of 2-propanol was added dropwise. After the addition was complete, the reaction was stirred at reflux for an additional 8 h and then cooled to 0 °C. The mixture was diluted with 100 mL of ether

and poured into 300 mL of ice-cold water. The aqueous layer was separated, saturated with NaCl, and extracted with 50 mL of ether (3x). The combined organic layers were washed with NaCl (2x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure to give a yellow oil. Vacuum distillation of the oil yielded 17.6 g (75.8 mmol, 77%) of a pale yellow oil containing **38** and **39**, bp 102-107 °C (0.1 mm Hg).

(1*R*,2*SR*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexylacetate (40). In a 500-mL, three-necked, round-bottomed flask fitted with a reflux condenser carrying a $CaCl_2$ drying tube, a 125-mL addition funnel, and a magnetic stir bar was added 37.3 g (161 mmol) of the mixture of **38** and **39**, 1.95 g (16.0 mmol) of DMAP, and 24.3 g (33.5 mL, 240 mmol) of TEA in 125 mL methylene chloride. The stirred solution was cooled to 0 °C and 36.1 g (25.5 mL, 320 mmol) of chloroacetyl chloride in 75 mL of methylene chloride was added over 2 h. After the addition was complete, the reaction was stirred at 0 °C for an additional 8 h and at room temperature for 36 h. The solution was concentrated under reduced pressure to a volume of approximately 50 mL and then dissolved in 100 mL of ether. The organic solution was washed with 1 M HCl (3x), $NaHCO_3$ (2x), NaCl (1x), dried ($MgSO_4$), vacuum filtered to remove solids, and concentrated under reduced pressure. The resulting yellow oil was dissolved in 50 mL of anhydrous ethanol and cooled to initiate crystallization. The resulting crystals were isolated by vacuum filtration and recrystallized from anhydrous ethanol. Isolation of the resulting white crystals afforded 21.8 g (70.7 mmol, 44%) of chloroacetate **40**, mp 77-79 °C, (lit mp 82-83 °C); $[\alpha]_D^{23} = +22.5$ ° ($c = 2.3$, CCl_4). IR 1760 cm^{-1}; ^1H NMR δ 7.33-7.26 (complex, 3 H), 7.17-7.11 (complex, 2 H), 4.90 (td, J = 10.9, 4.6 Hz, 1 H), 3.35 (d, J = 14.9 Hz, 1 H), 3.01 (d, J = 15.0 Hz, 1 H), 2.08 (tm, J = 11.4 Hz, 1 H), 1.93-1.81

(complex, 2 H), 1.73 (m, 1 H), 1.59-0.85 (complex, 13 H); ^{13}C NMR δ 166.5, 151.7, 128.0, 125.3, 125.1, 75.8, 50.2, 41.5, 40.8, 39.4, 34.4, 31.2, 29.8, 26.2, 22.6, 21.7.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (1). In a 1000-mL, three-necked, round-bottomed flask fitted with a reflux condenser and a magnetic stir bar was placed 21.6 g (70.0 mmol) of **40** dissolved in a solution of 700 mL of 90% ethanol, and 7.84 g (0.14 mol) of potassium hydroxide pellets. The solution was heated at reflux for 8 h and then concentrated under reduced pressure to a volume of approximately 100 mL. To this solution was added 250 mL of ether and 100 mL of water. The aqueous phase was separated, saturated with NaCl and extracted with 50 mL of ether (2x). The combined organic layers were extracted with NaCl (1x), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Vacuum distillation afforded 14.6 g (62.9 mmol, 90%) of (-)-8-phenylmenthol (**1**) as a colorless oil, bp 105-108 °C (0.05 mm); $[\alpha]^{23}_D = -26$ ° (*c* = 1.4, EtOH); IR 3570, 3407 cm^{-1}; ^{1}H NMR δ 7.39 (d, *J* = 7.2 Hz, 2 H), 7.32 (t, *J* = 6.9 Hz, 2 H), 7.18 (t, *J* = 7.0 Hz, 1 H), 3.53 (qd, *J* = 9.7, 4.3 Hz, 1H), 1.84 (m, 1 H), 1.76-1.59 (complex, 3 H), 1.45-1.29 (complex, 7 H), 1.21-0.83 (complex, 7 H); ^{13}C NMR δ 151.2, 128.4, 125.7 (2), 72.9, 54.1, 45.3, 39.7, 34.8, 31.4, 28.6, 26.4, 24.2, 22.0.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl 2-Nitrophenylacetate (43). In a 250-mL, round-bottomed flask containing a magnetic stir bar and fitted with a reflux condenser carrying a $CaCl_2$ drying tube was placed 2.00 g (11.0 mmol) of **41** and 15.0 mL of thionyl chloride. The mixture was refluxed for 8 h, while ensuring that the temperature of the oil bath did not exceed 80 °C. Excess thionyl chloride was removed by addition of 25 mL of benzene followed by distillation under reduced pressure. This procedure was

repeated three times to yield 2.10 g (10.6 mmol, 96%) of 2-nitrophenylacetyl chloride (**42**) as a red oil that was used without further purification.

In a 100-mL, three-necked, round-bottomed flask fitted with a reflux condenser carrying a $CaCl_2$ drying tube, a 125-mL addition funnel, and a magnetic stir bar was added 1.50 g (6.47 mmol) of **1**, 90 mg (0.74 mmol) of DMAP, and 1.07 g (1.47 mL, 10.6 mmol) of TEA in 40 mL methylene chloride. The stirred solution was cooled to 0 °C and 2.10 g (10.6 mmol) of **42** in 20 mL of methylene chloride was added over 1 h. After the addition was complete, the reaction was stirred at 0 °C for an additional 8 h and then at room temperature for 36 h. The solution was concentrated under reduced pressure to a volume of approximately 10 mL and then dissolved in 25 mL of ether. The solution was washed with 1 M HCl (3x), $NaHCO_3$ (2x), NaCl (1x), dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure. The resulting oil was chromatographed on a 50 cm x 2 cm silica gel column eluted with increasing concentrations of ether in hexane (0-5%) to yield 2.25 g (5.69 mmol, 88%) of **43**. IR 1732, 1530, 1349 cm^{-1}; ^1H NMR δ 8.06 (dd, J = 8.1, 1.3 Hz, 1 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.46-7.15 (complex, 7 H), 4.84 (td, J = 10.6, 4.4 Hz, 1 H), 3.52 (d, J = 17.3 Hz, 1 H), 3.19 (d, J = 17.3 Hz, 1 H), 2.04 (tm, J = 10.9 Hz, 1 H), 1.87 (m, 1 H), 1.82-1.60 (complex, 2 H), 1.42-0.90 (complex, 8 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 169.2, 151.8, 148.8, 133.3, 133.2, 129.9, 128.4, 127.9, 125.7, 125.5, 125.1, 75.2, 50.1, 41.4, 39.6, 39.3, 34.5, 31.3, 28.5, 26.4, 24.2, 21.8; HRMS *m/z*: Calcd for $C_{24}H_{29}NO_4$: 395.2096; Found: 395.2095.

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.91; H, 7.34. Found: C, 72.68; H, 7.45.

Representative Procedure for Conjugate Addition Reactions: (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2-Nitrophenyl)-5-oxohexanoate (46, 47). The general procedure of

Makosza and Tyrala[34] was adapted. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar was charged with 40 mL of dry acetonitrile, 8 mg of 18-crown-6 and 3.48 g (25.2 mmol) of anhydrous potassium carbonate. Stirring was started and 1.19 g (3.00 mmol) of **43** was added. The mixture was cooled to 0 °C and 0.32 g (4.50 mmol) of **44** was added. The solution was allowed to warm to room temperature over 48 h and then filtered to remove solids. Concentration gave a yellow oil that was purified by PTLC using increasing concentrations of ether in hexanes (5-15%) to yield 0.89 g (1.9 mmol, 64%) of **46** and **47** as a white solid (5:1). The mp of the diastereomeric mixture was 114-116 °C. Spectral data for the major diastereomer (**46**): IR 1725, 1535, 1353 cm^{-1}; ^1H NMR δ 7.85 (d, J = 8.1 Hz, 1 H), 7.56 (t, J = 7.8 Hz, 1 H), 7.49-7.08 (complex, 7 H), 4.77 (td, J = 10.8, 4.4 Hz, 1 H), 3.74 (dd, J = 8.2, 6.6 Hz, 1 H), 2.44-1.89 (complex, 10 H), 1.66-1.38 (complex, 4 H), 1.26-1.16 (complex, 5 H), 1.07 (s, 1 H), 1.01 (s, 1 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 207.3, 171.2, 151.0, 132.8, 132.7, 130.3, 129.5, 128.1, 125.4, 125.2, 125.1, 124.6, 76.2, 50.2, 45.5, 41.5, 41.2, 39.7, 34.4, 31.3, 29.9, 26.8, 26.4 (2), 26.1, 21.7; HRMS *m/z*: Calcd for $C_{28}H_{35}NO_5$: 465.2515; Found: 465.2513.

Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01. Found: C, 72.54; H, 7.66; N, 2.80.

(1*R*,2*S*,5*R*) -8- Phenylmenthyl - (2-Nitrophenyl) -5- oxoheptanoate (48, 49). 0.60 g (1.25 mmol, 58%, diastereomeric ratio 3:1); Spectral data for the major diasteromer (**48**): IR 1725, 1713, 1526, 1353 cm^{-1}; ^1H NMR δ 7.85 (d, J = 8.1 Hz, 1 H), 7.59-7.08 (complex, 8 H), 4.78 (td, J = 10.6, 3.7 Hz, 1 H), 3.76 (dd, J = 8.4, 6.5 Hz, 1 H), 2.51-1.84 (complex, 12 H), 1.69-0.76 (complex, 14 H); ^{13}C NMR δ 210.3, 171.3,

151.3, 132.9, 132.8, 130.3, 129.6, 128.1, 125.5, 125.4, 125.2, 124.6, 76.2, 50.2, 45.6, 41.6, 39.9, 39.5, 35.8, 34.4, 31.3, 28.3, 26.5, 26.4, 26.2, 24.4, 21.7; HRMS *m/z*: Calcd for $C_{29}H_{37}NO_5$: 479.2671; Found: 479.2669.

Anal. Calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92. Found: C, 72.89; H, 7.87; N, 2.73.

Representative Procedure for Reduction-Reductive Amination: (1*R*, 2*S*, 5*R*)-8-Phenylmenthyl (2*R,5*S**)-2-Methyl- 2, 3, 4, 5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (50).** To a solution of 0.89 mg (1.91 mmol) of **46/47** in 150 mL of methanol was added 300 mg of 5% palladium-on-carbon. The mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atm of hydrogen at 30 °C for 3 h. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite topped with a layer of $MgSO_4$ to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by PTLC using increasing concentrations of ether in hexanes (5-50%) to give 2 bands. Band 2 (from the top) gave 390 mg (0.93 mmol, 49%); IR 3350, 1722 cm^{-1}; ^1H NMR δ 7.35-6.93 (complex, 7 H), 6.85 (t, J = 7.3 Hz, 1 H), 6.69 (d, J = 7.7 Hz, 1 H), 4.89 (td, J = 10.7, 4.3 Hz, 1 H), 3.03 (dd, J = 5.8, 3.0 Hz, 1 H), 2.73 (m, 1H), 2.06 (m, 2 H), 1.90 (m, 1 H), 1.77-0.93 (complex, 22 H), 0.87 (d, J = 10.0 Hz, 3 H); ^{13}C NMR δ 171.9, 151.9, 148.8, 131.5, 130.6, 127.8, 125.4, 125.3, 124.9, 121.1, 120.8, 74.4, 53.8, 50.5, 50.2, 41.7, 39.5, 35.3, 34.5, 31.2, 28.3, 28.2, 26.5, 24.3, 24.2, 21.7; HRMS *m/z*: Calcd for $C_{28}H_{37}NO_2$: 419.2824; Found: 419.2823.

Anal. Calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.45; H, 8.97; N, 3.21.

(1*R*,2*S*,5*R*) -8-Phenylmenthyl (2*S*, 5*S*) -2-Methyl- 2, 3, 4, 5-tetrahydro -1*H*- 1-benzazepine-5-carboxylate (51). Band 1: 30 mg (0.072 mmol, 4%); IR 3350, 1716 cm^{-1}; ^1H NMR δ 7.31-7.14 (complex, 5 H), 7.07-7.01 (complex, 2 H), 6.78 (m, 1 H), 6.66 (d, J = 8.1 Hz, 1 H), 4.83 (td, J = 10.6, 4.5 Hz, 1 H), 3.19 (dd, J = 6.8, 3.4 Hz, 1 H), 2.94 (m, 1 H), 2.20 (m, 1 H), 1.80 (m, 2 H), 1.67-0.86 (complex, 18 H), 0.80 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 172.7, 151.4, 148.2, 130.8, 130.4, 127.8, 127.4, 125.5, 125.0, 120.7, 120.2, 74.2, 53.1, 50.1, 49.3, 41.1, 39.8, 34.4, 34.1, 31.4, 27.3, 26.7, 26.6, 26.5, 23.9, 21.8; HRMS *m/z*: Calcd for $C_{28}H_{37}NO_2$: 419.2824; Found: 419.2822.

Anal. Calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.43; H, 8.95; N, 3.25.

Reduction-Reductive Amination of (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-(2-Nitrophenyl)-5-oxoheptanoate (48): (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R,5*S**)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (52).** Band 2 (from the top): 300 mg (0.69 mmol, 55%); IR 3367, 1716 cm^{-1}; ^1H NMR δ 7.34-6.95 (complex, 7 H), 6.86 (t, J = 7.4 Hz, 1 H), 6.71 (d, J = 7.8 Hz, 1 H), 4.84 (td, J = 10.6, 4.6 Hz, 1 H), 3.05 (dd, J = 5.9, 2.9 Hz, 1 H), 2.46 (m, 1 H), 2.11-0.80 (complex, 26 H); ^{13}C NMR δ 172.0, 152.0, 148.9, 131.4, 131.0, 127.9, 127.2, 125.4, 125.0, 121.2, 120.8, 74.5, 59.9, 57.0, 50.5, 50.3, 41.8, 39.6, 34.6, 33.0, 31.3, 30.4, 28.3, 26.6, 24.4, 21.8, 10.8; HRMS *m/z*: Calcd for $C_{29}H_{39}NO_2$: 433.2981; Found: 433.2980.

Anal. Calcd for $C_{29}H_{39}NO_2$: C, 80.33; H, 9.06; N, 3.23. Found: C, 80.64; H, 9.14; N, 3.06.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl(2*S,5*S**)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (53).** Band 1 (from the top): 45 mg (0.10 mmol, 8%); IR 3367,

1716 cm^{-1}; ^1H NMR δ 7.31-7.13 (complex, 6 H), 7.04 (m, 1 H), 6.78 (m, 1 H), 6.67 (d, *J* = 7.7 Hz, 1 H), 4.84 (td, *J* = 10.6, 4.3 Hz, 1 H), 3.19 (dd, *J* = 7.2, 3.2 Hz, 1 H), 2.71 (m, 1 H), 2.19 (m, 1 H), 1.84-1.24 (complex, 16 H), 1.23 (s, 3 H), 1.16 (s, 3 H), 0.81(d, *J* = 6.5 Hz, 3 H); ^{13}C NMR δ 172.9, 151.4, 148.2, 130.4 (2), 127.9, 127.4, 125.5, 125.0, 120.6, 120.1, 74.2, 58.9, 57.0, 50.1, 49.2, 41.2, 39.8, 34.4, 31.8, 31.2, 30.0, 27.2, 26.7, 26.4, 21.8, 10.6; HRMS *m/z*: Calcd for $C_{29}H_{39}NO_2$: 433.2981; Found: 433.2979.

Anal. Calcd for $C_{29}H_{39}NO_2$: C, 80.33; H, 9.06; N, 3.23. Found: C, 80.29; H, 9.08; N, 3.24.

(2*R, 5*S**) -2-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-methanol (54).** The general procedure of Tolvanen and co-workers[53] was followed. A suspension of 44 mg (1.60 mmol) of lithium aluminum hydride in 40 mL of dry tetrahydrofuran was prepared and cooled to 0 °C. To the suspension was added 130 mg (0.31 mmol) of **50** in 10 mL of dry tetrahydrofuran. The mixture was stirred and warmed to room temperature. The progress of the reaction was followed by TLC. After 8 h, 20 mL of saturated sodium sulfate solution was cautiously added and the mixture was vacuum filtered through Celite. The filter cake was rinsed with 25 mL of methylene chloride, an additional 25 mL of methylene chloride was added to the filtrate and the mixture was washed with saturated NaCl solution. The aqueous layer was saturated with NaCl and was further extracted with methylene chloride (2x). The combined organic layers were washed with NaCl, dried ($MgSO_4$), vacuum filtered, and concentrated under reduced pressure to give a light yellow oil which was purified by PTLC using increasing concentrations of ether in hexanes (15-50%) to give 30 mg (0.17 mmol, 55%) of **54**. IR 3555, 3336 cm^{-1}; ^1H NMR δ 7.11-7.05 (complex, 2 H), 6.89 (t, *J* = 7.2 Hz, 1 H), 6.74 (d, *J* = 7.7 Hz, 1 H),

4.01 (dd, J = 10.5, 6.1 Hz, 1 H), 3.90 (dd, J = 10.5, 5.6 Hz, 1 H), 3.02 (m, 1 H), 2.95 (m, 1 H), 2.07 (m, 1 H), 1.82-1.67 (complex, 3 H), 1.27 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 148.2, 133.8, 131.5, 127.5, 121.9, 120.9, 65.5, 54.4, 48.0, 34.5, 29.2, 24.2; HRMS *m/z*: Calcd for $C_{12}H_{17}NO$: 191.1310; Found: 191.1308.

Anal. Calcd for $C_{17}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.55; H, 9.07; N, 7.21.

(1*R*, 2*S*, 5*R*)-8-Phenylmenthol (1). 40 mg (0.17 mmol, 55%) was also recovered from the PTLC plate, $[\alpha]_D^{23}$ = -26° (c = 0.31, EtOH).

Acknowledgements. Support of this work by the NIH (GM54256) and by the Oklahoma Center for the Advancement of Science and Technology (HR01-015) was greatly appreciated. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

REFERENCES

1. Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, NY, 1979; pp 113-137.
2. Kloetzel, M. C. *J. Am. Chem. Soc.* **1947**, *69*, 2271-2275.
3. Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844-3850.
4. Masamune, T.; Takasugi, M.; Suginome, H.; Yokyama, M. *J. Org. Chem.* **1964**, *29*, 681-685.
5. Kupchan, S. M.; Merianos, J. J. *J. Org. Chem.* **1968**, *33*, 3735-3738.
6. Gutsche, C. D.; Zandstra, H. R. *J. Org. Chem.* **1974**, *39*, 324-330.
7. Sicker, D.; Reifegerste, D.; Hauptmann, S.; Wilde, H.; Mann, G. *Synth. Commun.* **1985**, 331-333.
8. Maeda, H.; Selvakumar, N.; Kraus, G. A. *Tetrahedron* **1999**, *55*, 943-954.
9. Degnan, A. P.; Meyers, A. I. *J. Org Chem.* **2000**, *65*, 3503-3512.
10. Benchekroun-Mounir, N.; Dugat, D.; Gramain, J. C.; Husson, H. P. *J. Org. Chem.* **1993**, *58*, 6457-6465.
11. Artico, M.; DeMartino, G.; Filacchioni, G.; Giuliano, R. *Farmaco Ed. Sci.* **1969**, *24*, 276-284.
12. Betancourt, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737-3740.
13. Ventrice, T.; Campi, E. M.; Jackson, W. R.; Patti, A. F. *Tetrahedron* **2001**, *57*, 7557-7574.
14. (a) Hockless, D. C. R.; Lindoy, L. F.; Swiegers, G. F.; Wild, S. B. *J. Chem. Soc. Perkin Trans. 1* **1998**, *117-122* (b) Gugger, P. A.; Hockless, D. C. R.; Swiegers, G. F.; Wild, S. B. *Inorg. Chem.* **1994**, *33*, 5671-5677.

15. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, Vol. 11; Wiley: New York, NY, 1994; pp 675-684.

16. Zhao, D. L. B.; LaVoie, E. J. *J. Org. Chem.* **2000**, *65* 2802-2805.

17. Topliss, J. G.; Shapiro, E. P.; Taber, R. I. *J. Med Chem.* **1967**, *10*, 642-646.

18. Elliot, R. D.; Temple, C.; Montgomery, J. A. *J. Org. Chem.* **1968**, *33*, 533-536.

19. Paterne, M.; Brown, E. *J. Chem. Res. (S)* **1985**, 278-279.

20. Chavdarian, C. G.; Seeman, J. I., Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492-494.

21. Hesse, M. *Alkaloid Chemistry*; J. Wiley and Sons: New York, 1978.

22. De Kempe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705-3718.

23. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595-3607.

24. Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847-2850.

25. Crabb, T. A.; Canfield, L. M.; Bowen, D. *J. Chem Soc. Perkin Trans. 1* **1994**, 9-13.

26. Zimmerman, H. E.; Bunce, R. A. *J. Org. Chem.* **1982**, *47*, 3377-3396.

27. Cousseau, J. *Synthesis*, **1980**, 805-806.

28. Dauben, W. G.; Cogen, J. M.; Ganzer, G. A.; Behar, V. J. *J. Am. Chem. Soc.* **1991**, *113*, 5817-5824.

29. Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634-3641.

30. Borowiecki, L.; Kaubski, A. *Pol. J. Chem.* **1978**, *52*, 1447-1455.

31. Hudlicky, T.; Ranu, B. C.; Naqvi, S. M.; Srnak, A. J. *J. Org. Chem.* **1985**, *50*, 123-127.

32. Ziegler, F. E.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987-3991.

33. Marvel, C. S.; Calvery, H. O. *Organic Syntheses;* J. Wiley and Sons, New York, NY; Coll. Vol. 1, **1941**, 533-545.

34. Qadir, M.; Priestly, R. E.; Rising, T. W. D. F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675-3678.

35. Makosza, M.; Tyrala, A. *Synth. Commun.* **1986**, *16*, 419-423.

36. Angle, S. R.; Rainier, J. D. *J. Org. Chem.* **1992**, 6883-6890.

37. (a) Besse, R.; Garratt, P. J.; Hobbs, C. J.; Rogers, H. M.; Sueleiman, A. M. *Tetrahedron* **1990**, *46*, 7803-7812 (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 3rd Ed.;* Plenum Press: New York, NY, 1990; pp 163-165. (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, N. Y., 1962; pp 198-202.

38. DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980,** *102*, 4505-4512.

39. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.

40. Tacconi, G.; Marione, F. *Ricerca Scientifica* **1968**, *38*, 1239-1244.

41. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

42. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.

43. Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953-964.

44. Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343-5346.

45. Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed.* **1987**, *26*, 1167-1169.

46. Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413-5415.

47. Nouguier, R.; Béraud, V.; Vanelle, P.; Crozet, M. P. *Tetrahedron Lett.* **1999**, *40*, 5013-5014.

48. Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025-5028.

49. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.

50. Bosch, J.; Bennasar, M. L. *Synlett* **1995**, 587-596.

51. Bennasar, M. L.; Zulaica, E.; Alonso, Y.; Vidal, B.; Vazquez, J. T.; Bosch, J. *Tetrahedron Asymm.* **2002**, *13*, 95-106.

52. Ort, O. *Organic Synthesis* **1987**, *65*, 203-214.

53. Rönköö, K.; Berner, M.; Jokela, R.; Tolvanen, A. *J. Heterocyclic Chem.* **2000**, *37*, 1145-1149.

54. Amputch, M. A.; Matamoros, R.; Little, R. D. *Tetrahedron* **1994**, *50*, 5591-5614.

55. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992; pp 5-27.

56. Osterlof, J. *Acta. Chem. Scan.* **1950**, *4*, 374-385.

CRYSTAL DATA AND STRUCTURE REFINEMENT FOR (±)-(5*S,2*R**)-2-METHYL-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

Empirical formula	$C_{13}H_{17}NO_2$
Formula weight	219.28
Temperature	293 (2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2/c
Unit cell dimensions	a = 9.312(13) A alpha = 90 deg
	b = 14.805(11) A beta = 102.48(4) deg
	c = 9.373(6) A gamma = 90 deg
Volume	1262(2) A^3
Z, Calculated density	4, 1.154 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	472
Crystal size	0.1 x 0.1 x 0.1 mm
Theta range for data collection	2.24 to 30.00 deg
Index ranges	-13<=h<=1, -20<=k<=20, -8<=1<=10
Reflections collected / unique	4469 / 2241 [R(int) = 0.0700]
Completeness to 2theta = 30.00	58.7%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2241 / 0 / 146
Goodness-of-fit on F^2	0.839
Final R indices [I>2sigma (I)]	R1 = 0.0628, wR2 = 0.1041
R indices (all data)	R1 = 0.1845, wR2 = 0.1606
Largest diff. peak and hole	0.140 and –0.178 e.A^-3

ATOMIC COORDINATES AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS FOR (±)-(5*S,2*R**)-2-METHYL-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

	x	y	z	U (eq)
C(1)	2900(4)	5551(2)	115(6)	48(1)
N(2)	3480(3)	4650(2)	192(4)	51(1)
C(3)	2492(4)	3858(2)	174(6)	62(2)
C(3′)	3422(5)	3062(2)	898(6)	82(2)
C(4)	1676(5)	3608(3)	-1364(7)	71(2)
C(5)	585(4)	4319(3)	-2157(6)	73(2)
C(6)	1282(4)	5240(3)	-2466(6)	62(2)
C(7)	1823(4)	5842(2)	-1140(6)	55(2)
C(8)	1307(4)	6742(3)	-1137(6)	70(2)
C(9)	1850(5)	7347(3)	-24(7)	76(2)
C(10)	2950(4)	7069(3)	1166(7)	75(2)
C(11)	3470(4)	6177(2)	1216(6)	61(2)
C(12)	2479(4)	5118(3)	-3407(7)	55(2)
C(13)	2962(5)	4468(3)	-5580(7)	87(2)
O(12)	3702(3)	5466(2)	-3138(4)	71(1)
O(12′)	1986(3)	4580(2)	-4557(5)	80(2)

BOND LENGTHS (Å) FOR (±)-(5*S,2*R**)-2-METHYL-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

Bond Length	Å
C(1) – (C11)	1.403(6)
C(1) – N(2)	1.435(4)
C(1) – C(7)	1.437(6)
N(2) – C(3)	1.488(4)
C(3) – C(4)	1.523(7)
C(3) – C(3′)	1.532(5)
C(4) – C(5)	1.539(6)
C(5) – C(6)	1.563(5)
C(6) – C(7)	1.524(7)
C(6) – C(12)	1.575(7)
C(7) – C(8)	1.417(5)
C(8) – C(9)	1.385(7)
C(9) – C(10)	1.404(7)
C(10) – C(11)	1.405(5)
C(12) – O(12)	1.225(4)
C(12) – O(12′)	1.339(6)
C(13) – O(12′)	1.466(6)

BOND ANGLES FOR (±)-(5*S,2*R**)-2-METHYL-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

Bond	Angle (°)
C(11) – C(1) – N(2)	119.9(4)
C(11) – C(1) – C(7)	119.3(3)
N(2) – C(1) – C(7)	120.6(4)
C(1) – N(2) – C(3)	120.4(3)
N(2) – C(3) – C(4)	112.6(4)
N(2) – C(3) – C(3′)	108.2(3)
C(4) – C(3) – C(3′)	110.5(4)
C(3) – C(4) – C(5)	115.6(4)
C(4) – C(5) – C(6)	115.5(3)
C(7) – C(6) – C(5)	115.9(4)
C(7) – C(1) – C(8)	112.0(3)
C(7) – C(6) – C(12)	112.1(4)
C(5) – C(6) – C(12)	117.3(4)
C(8) – C(7) – C(1)	120.0(4)
C(8) – C(7) – C(6)	122.7(3)
C(9) – C(8) – C(7)	122.8(5)
C(8) – C(9) – C(10)	119.6(4)
C(9) – C(10) – C(11)	119.3(5)
C(1) – C(11) – C(10)	121.6(4)
O(12) – C(12) – O(12′)	123.9(5)
O(12) – C(12) – C(6)	125.1(5)
O(12′) – C(12) – C(6)	111.0(4)
C(12) – O(12′) – C(13)	116.1(4)

ANISOTROPIC DISPLACEMENT PARAMETERS FOR (±)-(5*S,2*R**)-2-METHYL-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

	U11	U22	U33	U23	U13	U12
C(1)	52(2)	47(2)	42(5)	-4(2)	12(2)	-4(2)
N(2)	52(2)	47(2)	53(4)	0(2)	8(1)	1(1)
C(3)	66(3)	49(2)	72(6)	1(3)	17(2)	-8(2)
C(3′)	101(4)	55(2)	90(7)	4(3)	22(3)	1(2)
C(4)	87(3)	57(2)	71(7)	-8(3)	20(3)	-24(2)
C(5)	71(3)	89(3)	59(6)	-16(3)	10(2)	-25(2)
C(6)	55(2)	72(3)	58(6)	4(3)	7(2)	3(2)
C(7)	55(2)	54(2)	54(6)	6(3)	9(2)	0(2)
C(8)	75(3)	62(2)	72(6)	9(3)	16(2)	14(2)
C(9)	95(4)	50(2)	84(7)	-1(3)	24(3)	9(2)
C(10)	80(3)	56(2)	89(7)	-19(3)	21(3)	-7(2)
C(11)	61(2)	55(2)	65(5)	-5(3)	9(2)	-5(2)
C(12)	70(3)	57(2)	34(6)	1(3)	2(2)	-1(2)
C(13)	102(4)	120(4)	41(8)	-30(4)	19(3)	-8(3)
O(12)	67(2)	83(2)	66(4)	-5(2)	16(2)	-16(1)
O(12′)	78(2)	110(2)	53(5)	-22(3)	19(2)	-14(2)

HYDROGEN COORDINATES AND ISOTROPIC DISPLACEMENT PARAMETERS FOR (±)-(*5S*,2R)-2-METHYL-2,3,4,5-TETRAHYDRO-*1H*-1-BENZAZEPINE-5-CARBOXYLATE (13)**

	x	y	z	U(eq)
H(2)	4421	4587	677	50
H(3A)	1778	4015	733	80
H(3'A)	2774	2560	918	50
H(3'B)	3904	3234	1871	50
H(3'C)	4315	2862	644	50
H(4A)	1167	3051	-1293	80
H(4B)	2395	3491	-1937	80
H(5A)	-160	4423	-1611	80
H(5B)	116	4066	-3083	80
H(6A)	511	5582	-3078	80
H(8A)	541	6941	-1932	80
H(9A)	1470	7952	-59	80
H(10A)	3347	7492	1927	80
H(11A)	4227	5983	2023	80
H(13A)	2510	4071	-6357	80
H(13B)	3138	5045	-5978	80
H(13C)	2879	4214	-5072	80

VITA

Lara Beth Johnson

Candidate for the Degree of

Doctor of Philosophy

Thesis: TANDEM REACTIONS FOR THE SYNTHESIS OF SUBSTITUTED TETRAHYDROQUINOLINE-4-CARBOXYLIC ESTERS AND RACEMIC AND CHIRAL SUBSTITUTED BENZAZEPINE-5-CARBOXYLIC ESTERS

Major Field: Chemistry

Biographical:

Personal Data: Born in Roswell, New Mexico on August 14, 1975, the daughter of Bonnie Innes and Dennis Johnson.

Education: Graduated from Victory Christian School, Tulsa, Oklahoma, in May 1993; received a Bachelor of Science degree in Biomedical Chemistry from Oral Roberts University, Tulsa, Oklahoma in May 1997. Completed the requirements for the Doctor of Philosophy degree with a major in Chemistry in December 2003.

Professional Experience: Graduate Teaching Assistant, General and Organic Chemistry Labs, Oklahoma State University, 1998-2003; Environmental Customer Service Representative, Waste Management Incorporated, Tulsa, Oklahoma, 1997-1998.

Professional Memberships: American Chemical Society, Phi Lambda Upsilon.