DISSERTATION

THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA ELECTROPHILIC GLYCINATES

Submitted by

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In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 1987

COLORADO STATE UNIVERSITY

April 13, 1987

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY PETER JOHN SINCLAIR ENTITLED "THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA ELECTROPHILIC GLYCINATES" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

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ABSTRACT

THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA ELECTROPHILIC GLYCINATES

A new asymmetric synthesis of α-monosubstituted-α-amino acids using D- and L-erythro-4-benzyloxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-ones **108** as amino acid templates is described. Bromination of **108** with NBS generates the key electrophilic glycinate **132** which couples with a variety of carbon nucleophiles with high diastereoselectivity to afford the amino acid precursors **134**. Catalytic hydrogenation of homologated heterocycles **134** directly furnishes the zwitterionic α-amino acids in high enantiomeric excess. Dissolving metal reduction of **134** permits the preparation of unsaturated amino acids while use of erythro-4-t-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one **160** allows the direct preparation of t-BOC protected α-amino acids. The synthetic approaches to a number of biologically interesting amino acids are described and mechanistic aspects of the coupling reaction are discussed.

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ACKNOWLEDGEMENT

There are many people who deserve my thanks for the support (both technical and otherwise) they provided during my stay at CSU. I thank the people who provided technical support, especially Don Dick and Suzie Miller for their invaluable assistance with the high field NMRs.

I would like to thank all of the graduate students and post-docs who offered assistance. They were ever generous in their distribution of knowledge, chemicals, and equipment. Thanks to Jose Toro who was a close companion and remains a close friend. Keith McDaniel helped me through the toughest period of graduate school. He offered support, encouragement and friendship, and never complained about the messy apartment. To him a special thank you.

The people in the Williams' group, both past and present, made the day-to-day routine enjoyable. I thank Mark and Lynn Kirms for their support and encouragement during the writing of this thesis. Mark's comments and suggestions on the first draft were invaluable. I also thank Paul Ehrlich for sharing many of the ups and downs of graduate school, and for the enjoyable discussions at the bench. Paul has been as good a friend and lab-mate as I could ask for. A special thanks to Rob Armstrong who made my first two years of graduate school as enjoyable and educational as any I've had. His companionship is missed.

A very special thanks goes to Rosalie Jaramillo who not only worked tirelessly and did a wonderful job typing and arranging this thesis but who also provided support, encouragement, and most important, a lasting friendship.

Finally, I would like to thank Professor Robert M. Williams, not only for financial support but also for providing me with an interesting project, guidance when needed and

freedom when appropriate. His interest in the project and my growth as a scientist is greatly appreciated.

DEDICATION

This dissertation is dedicated to my parents and family. Their constant love, support, and encouragement remind me of what is important and made this work possible and worthwhile.

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CHAPTER I

INTRODUCTION

A. Background

α-Amino acids are primary metabolites essential to life. The number of naturally occurring amino acids has grown substantially from the roughly 20 found in proteins to over 500 that are now known.[1] These compounds are remarkably varied in structure and this diversity has led to the utilization of many amino acids in stereoselective syntheses.[2] Moreover, amino acids exhibit a broad spectrum of physiological activity. As a result, these compounds are of tremendous biological interest, and many amino acids have been incorporated into peptide based pharmaceuticals.

The enormous synthetic utility and potential biological properties of rare and unnatural α-monosubstituted-α-amino acids has prompted researchers to pursue and develop efficient routes to these molecules. However, stereospecific syntheses and biological studies require the use of enantiomerically pure compounds. The goal, therefore, has been to devise expedient syntheses of the desired amino acids and obtain the product in high enantiomeric excess.

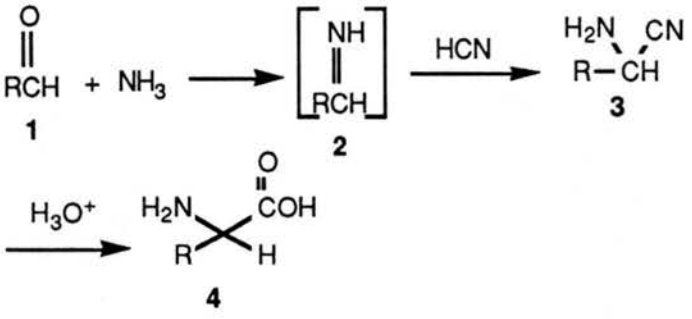
Traditional amino acid syntheses lead to racemic mixtures. Resolution methods can then be used to obtain the desired enantiomer. More recently there has been a great deal of effort involved in developing enantioselective syntheses that will furnish chiral, non-racemic α-amino acids directly. The following paragraphs briefly outline some of the more salient methods of racemic amino acid preparation.[3] In most cases only routes to α-monosubstituted-α-amino acids will be described.

B. Racemic Syntheses

Strecker Synthesis

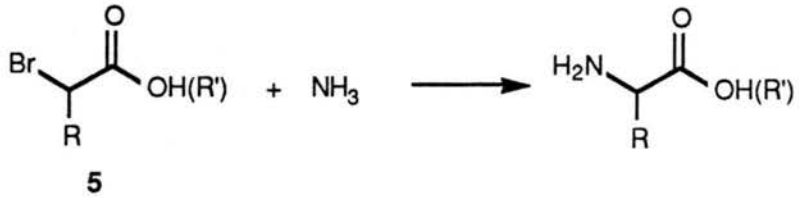
The first amino acid synthesis was developed over 100 years ago. In 1850 Strecker reported his flexible and efficient route to these compounds that still finds use today.[4] Condensation of an aldehyde (**1**) with ammonia and HCN gives the α-amino nitrile (**3**) via the imine (**2**). Hydrolysis affords the corresponding amino acid (**4**) (Scheme 1). Modifications of this route employ salts (NH_4Cl, KCN) to avoid the use of toxic HCN gas.

SCHEME 1



Nucleophilic Amination

A second amino acid synthesis that dates back to the 19th century is nucleophilic attack of ammonia on α-halo acids and esters (**5**) (Equation 1). This reaction provides one of the most straightforward methods of amino acid preparation. The α-halo acids can be obtained by classical procedures (e.g. Hell-Volhard-Zellinski bromination). A major side reaction is dialkylation of ammonia. This problem can be avoided by substituting hexamethylenetetraamine for ammonia and hydrolysing the initial adduct.

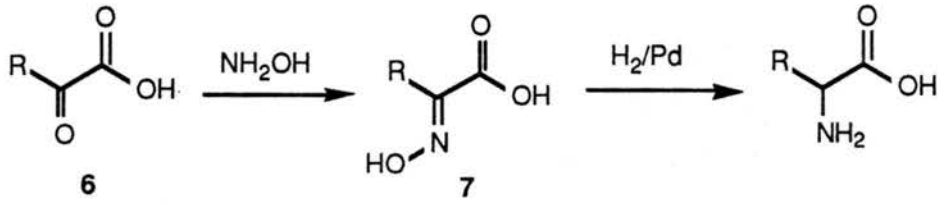


(Equation 1)

Reductive Amination

Akin to nucleophilic amination, reductive amination can be used in the synthesis of amino acids. An α-keto acid (**6**) will condense with hydroxylamine to give the corresponding oxime (**7**). Catalytic hydrogenation reduces the oxime moiety giving the α-amino acid directly (Scheme 2). This method is efficient, provided the α-keto acid is readily available, but precludes the synthesis of unsaturated amino acids.

SCHEME 2

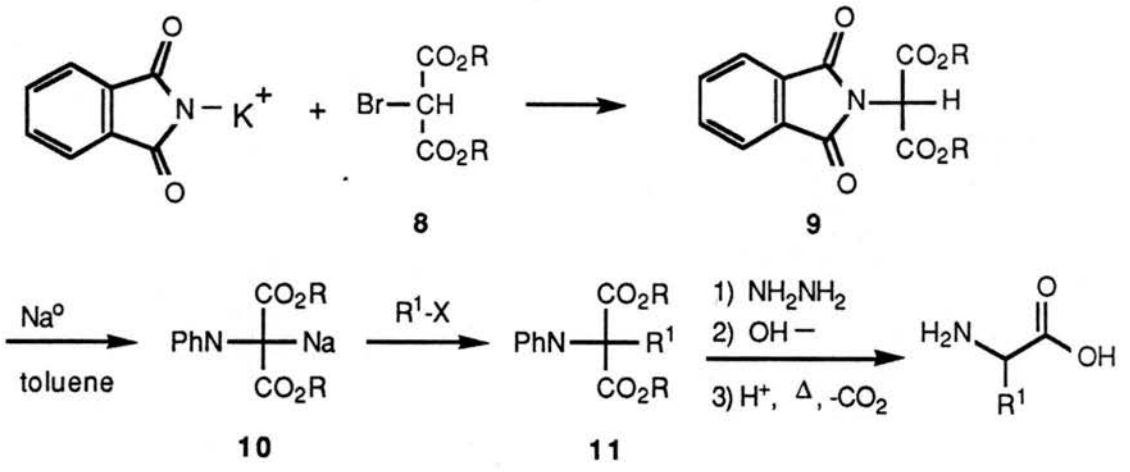


6 **7**

Alkylation of Nucleophilic Glycine Equivalents

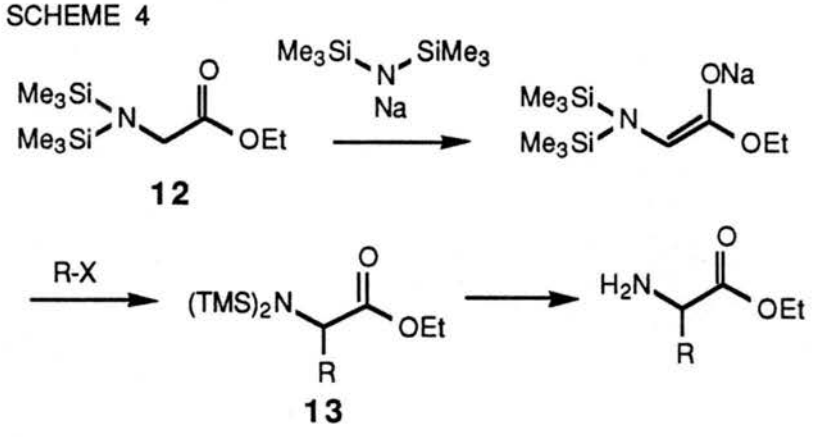
Nucleophilic glycinates have been used extensively as amino acid precursors. In 1905 Sörenson developed a synthesis based on the N-phthalimidomalonate **9** obtained by coupling potassium phthalimide with a dialkyl bromomalonate **8**.[5] Treatment of **9** with metallic sodium gives the sodiomalonate **10** that can couple with an alkyl halide giving **11**. Deprotection, hydrolysis and decarboxylation affords the desired amino acid (Scheme 3). The N-phthalimidomalonate has since been replaced by the N-formyl or N-acetyl derivatives as these protecting groups are more easily removed.

SCHEME 3



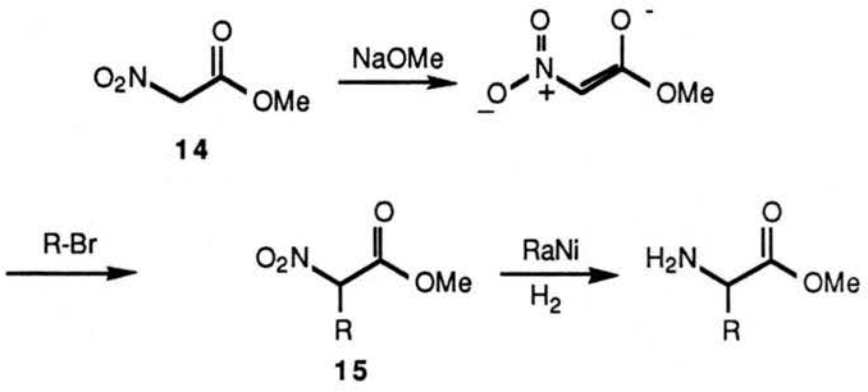
A more manifest glycine enolate is that derived from ethylglycinate, protected as the corresponding N,N-bis-(trimethylsilyl) derivative **12**. This compound can be converted to the enolate using sodium hexamethyldisilazide. Alkylation followed by hydrolysis affords the desired α-amino ester (Scheme 4).[6]

SCHEME 4



More recently, methyl nitroacetate **14** has been shown to undergo alkylation via its stabilized enolate to give nitroester **15**. The α-amino acid ester is then obtained upon reduction of the nitro group with Raney nickel (Scheme 5).[7]

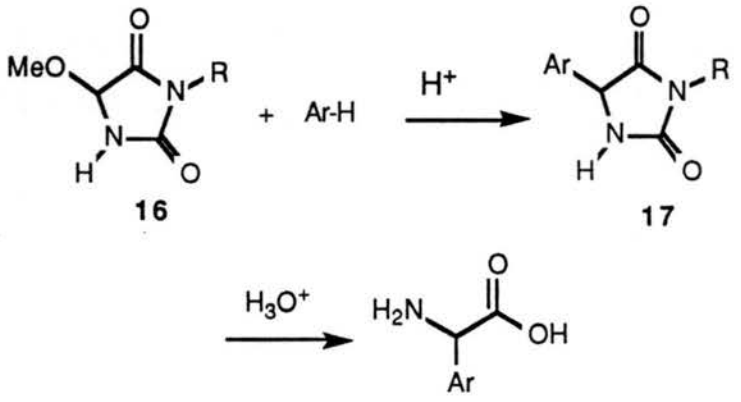
SCHEME 5



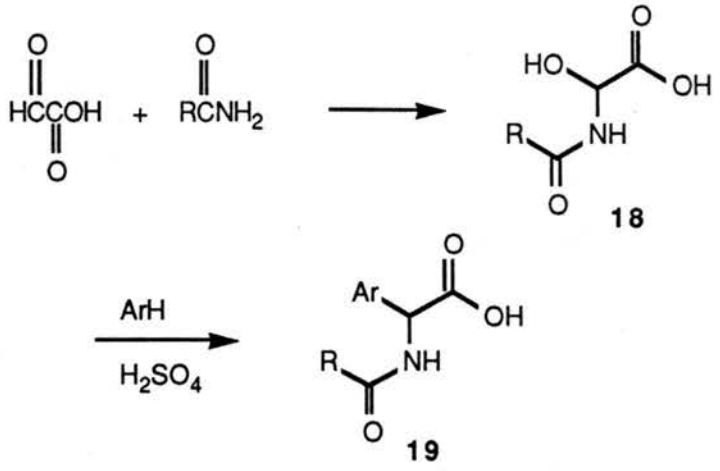
Electrophilic Glycine Equivalents

During the last thirty years electrophilic glycinates have been examined as α-amino acid precursors. Ben-Ishai demonstrated in 1970 that 5-methoxy hydantoins **16** will undergo acid catalyzed addition of aromatic compounds to give, upon hydrolysis of the heterocycle **17**, the aromatic amino acid (Scheme 6).[8] The cyclic structure of the hydantoin is not requisite for arylation. The acyclic glycolic acid amide adducts **18** will also arylate under acidic conditions to yield the corresponding N-acyl aromatic amino acids **19** directly (Scheme 7).[9]

SCHEME 6

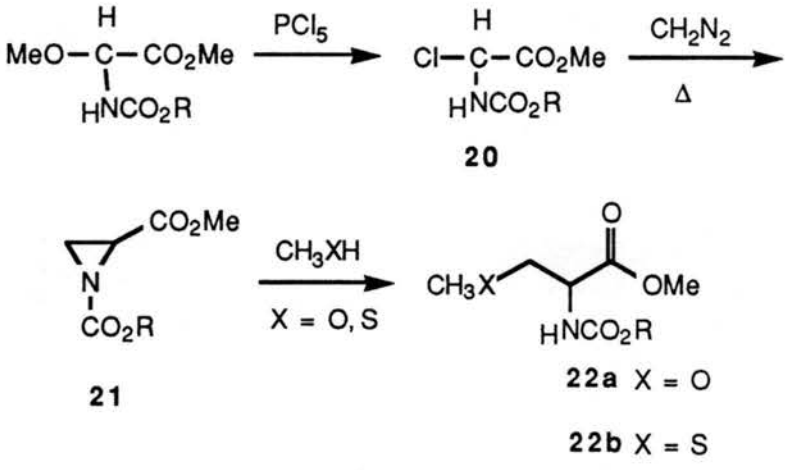


SCHEME 7



Ben-Ishai also prepared the 2-chloro-N-acyl glycinate **20**. Upon treatment with diazomethane and heat, aziridine **21** was formed. Ring opening with either CH_3OH or CH_3SH led to the O-methylserine **22a** and S-methyl cysteine **22b** derivatives respectively (Scheme 8).[10]

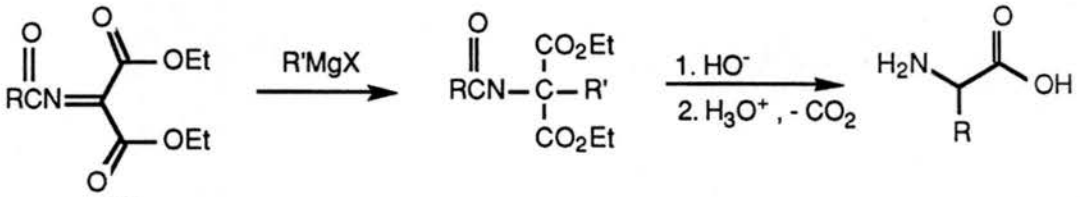
SCHEME 8



α-Imino acids likewise have been used as electrophilic glycinates. In 1982, Steglich reported the addition of Grignard reagents to the N-acyl imine of diethyl malonate **23**. The resulting compounds were hydrolysed and decarboxylated to yield the desired amino acid (Scheme 9).[11] Steglich used his electrophilic N-acyl amino malonate derivative

to prepare a variety of amino acids in high yields. This methodology complements the nucleophilic N-acyl amino malonate chemistry developed by Sörenson.

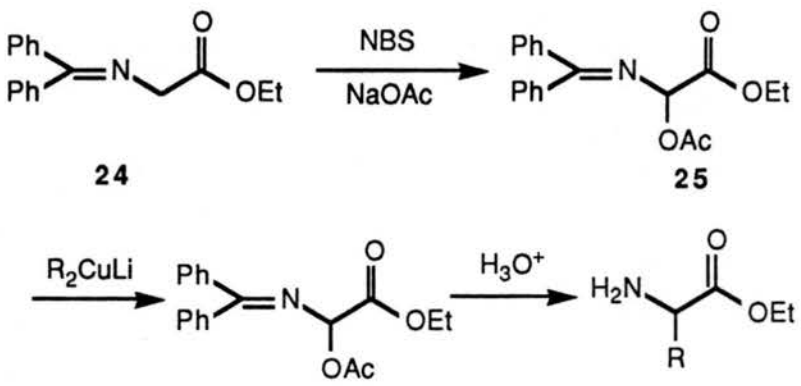
SCHEME 9



23

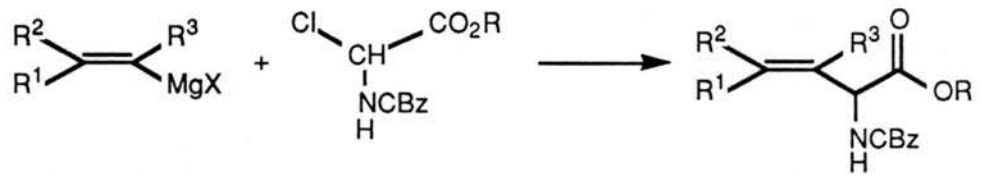
In 1985, O'Donnell reported the facile oxidation of the diphenylimine of ethyl glycinate **24** to yield the α-acetate **25**. Treatment of **25** with alkyl cuprates, followed by hydrolysis of the imine affords the desired amino acids in 40-71% yield (Scheme 10).[12] Using similar methodology, workers at Syntex have coupled vinyl Grignards with Ben-Ishai's 2-chloro-N-acyl glycinate **20** to prepare a variety of vinyl glycine derivatives **26**. Many of these compounds have been shown to be enzyme inhibitors (Scheme 11).[13]

SCHEME 10



24 **25**

SCHEME 11



20 **26**

The preparations described above are for the most part general and easy to carry out. They suffer only in that racemic mixtures are obtained. In order to prepare enantiomerically pure amino acids one must resort to resolution, thereby limiting the yield of the desired antipode to a maximum of 50%.[14] The traditional method of resolution involves the fractional crystallization of diastereomeric salts obtained upon treatment of the amino acid with an optically active base (e.g., brucine, quinine). This method can be time consuming and tedious. Furthermore, any new amino acid synthesized may require development of unique resolving conditions.

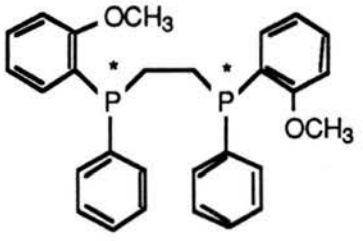
An advancement in resolution methods utilizes the enzymatic hydrolysis of the L-enantiomer of N-acyl-D,L-amino acids. The resulting free L-amino acid is easily separated from the N-acyl-D-amino acid by solvent extraction. This method suffers from narrow substrate specificity.

C. Enantioselective Syntheses

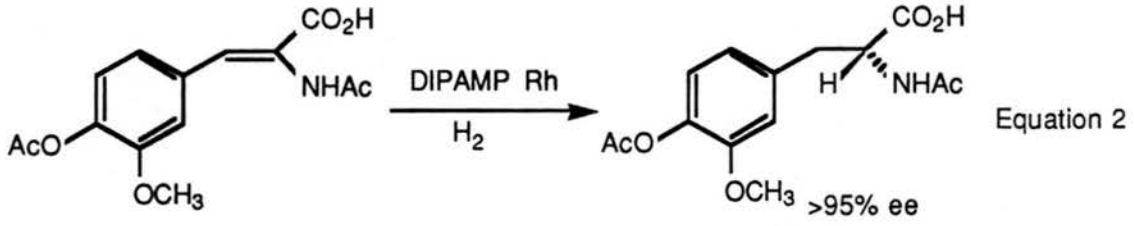
Due to the increased need for enantiomerically pure, rare and unnatural α-amino acids, coupled with the difficulties involved in the resolution of racemic mixtures, there has been a tremendous surge of interest in the development of enantioselective syntheses of these compounds. The methods that have been developed range from hydrogenation of dehydroamino acids to alkylation of activated chiral glycine equivalents. The following paragraphs provide a brief overview on some notable methods for the direct preparation of chiral, non-racemic α-monosubstituted α-amino acids.[15]

Hydrogenation of Dehydroamino Acids Using Chiral Catalysts

The efficient hydrogenation of dehydroamino acids to give enantiomerically pure α-amino acids has been the subject of vigorous research for the past twenty years.[16] The general methodology involves the homogenous catalytic hydrogenation of the amino acid precursor by a cationic rhodium catalyst (Wilkinson's catalyst) bearing a chiral phosphine ligand. Striking success has been realized in a number of cases. Monsanto's synthesis of D-DOPA, pioneered by Knowles, demonstrates the enormous potential of this methodology.[17] Hydrogenation of the Z-acetamidocinnamate ester **28** with a rhodium catalyst containing the DIPAMP **27** ligand takes place with high catalytic turnover to give the N-acyl-D-DOPA **29** in >95% enantiomeric excess (Equation 2).



DIPAMP
27



28 **29**

Equation 2

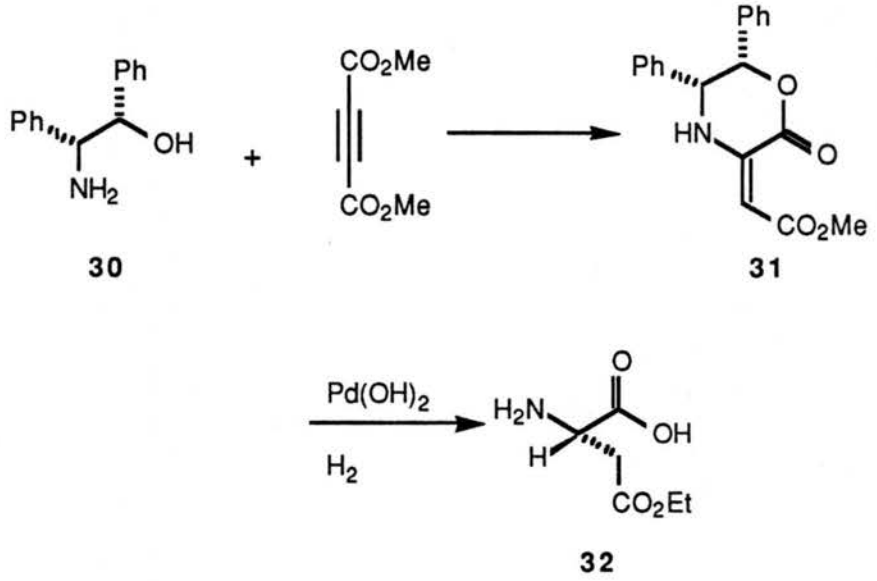
This route to amino acid preparation has the distinct advantage of needing the chiral auxiliary in only catalytic amounts. The conversion seems to work best with amino cinnamates to give phenylalanine derivatives. The principle disadvantage is its lack of

generality. Each amino acid synthesis requires the design of its own catalytic system in order to obtain good stereoselectivity.

Hydrogenation of Chiral Dehydroamino Acids

In 1968 Kagan prepared the 1,4-oxazin-2-one **31** by condensation of the L-erythro diphenyl amino alcohol **30** with dimethyl acetylenedicarboxylate. Heterogeneous hydrogenation using $Pd(OH)_2$ delivered hydrogen to the least hindered face of the molecule. Under these conditions the heterocycle is cleaved and the β-methyl ester of L-aspartic acid **32** was obtained in 98% e.e. (Scheme 12).[18] This route is very selective but is limited by the small number of amino acid precursors that can be prepared (only one amino acid was prepared).

SCHEME 12

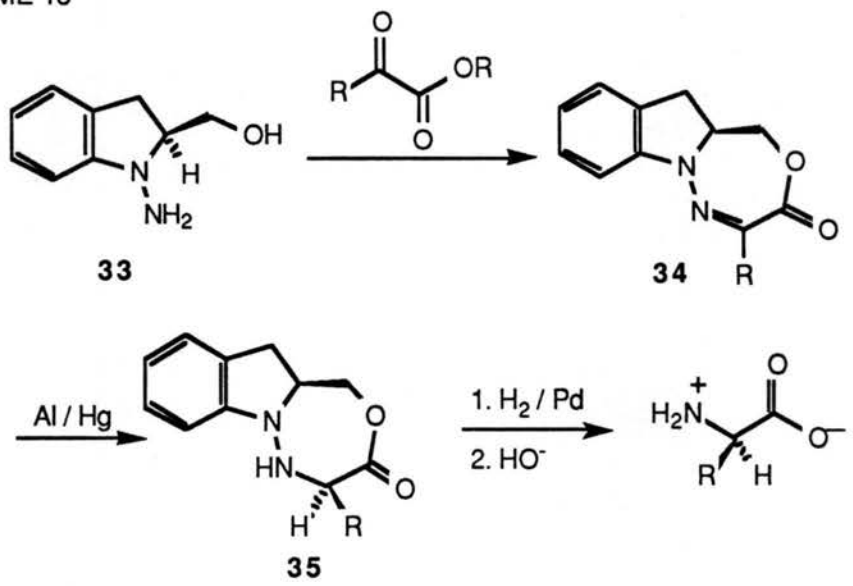


30 **31** **32**

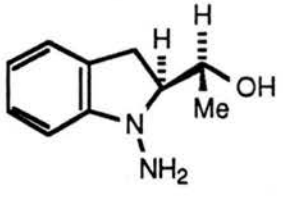
A second enantioselective amino acid synthesis based on chiral dehydro amino acids has been developed by Corey and coworkers. Their method is considerably more general than Kagan's with the added advantage of being able to recover and recycle the chiral auxiliary. Condensation of an α-keto acid with (2S)-N-amino-2-hydroxymethyl indoline **33** gives the tricylcic hydrazone **34**. Aluminum amalgam reduction occurs stereoselectively to give the hydrazine **35**. Catalytic hydrogenation cleaves the N-N bond

and the amino acid is freed upon hydrolysis (Scheme 13).[19] Using this scheme, alanine and butyrine were prepared in 80-90% optical purity. If intermediate **35** is recrystallized, alanine is obtained with ≥98% optical purity.

SCHEME 13



The overall stereoselectivity of this synthesis was increased by stereoselectively substituting a methyl group for one of the methylene hydrogens on the hydroxymethyl group. Thus, using **36** as the starting material allowed for the synthesis of a number of amino acids having optical purities of 97-98%.[20] All of the hydrogenation methods are limited in the type of functionality tolerated. Preparation of unsaturated amino acids is precluded.

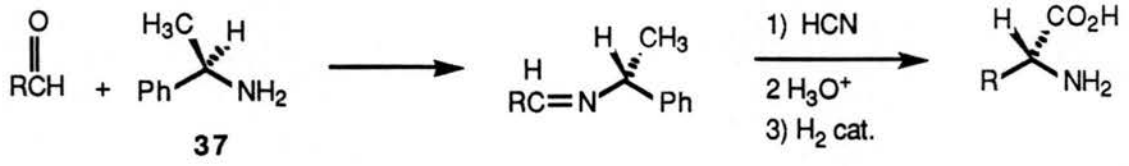


36

Asymmetric Strecker Synthesis

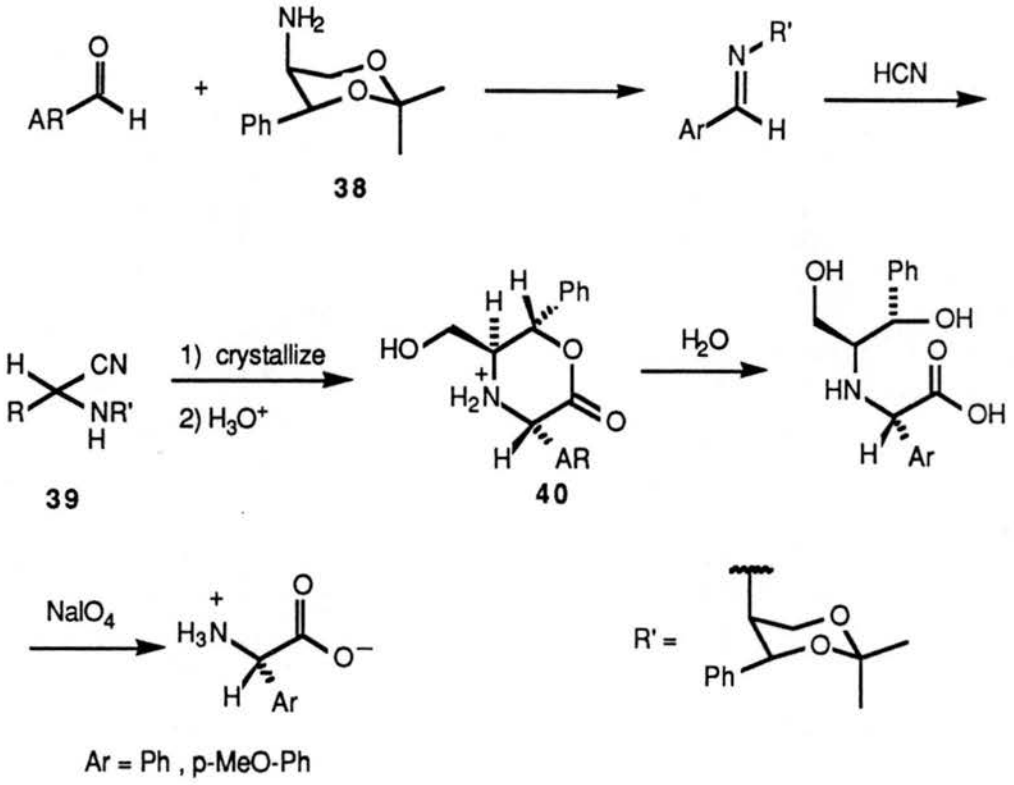
The use of chiral amines to induce stereoselection at the new stereogenic center formed during the Strecker synthesis has been known for over twenty years. The most common chiral auxiliary used in these reactions is α-methylbenzyl amine **37** (Scheme 14), which can be removed by hydrogenolysis. The amino acids typically are obtained in 20-60% e.e. Fractional crystallization allows for the preparation of amino acids of higher purity.[21]

SCHEME 14



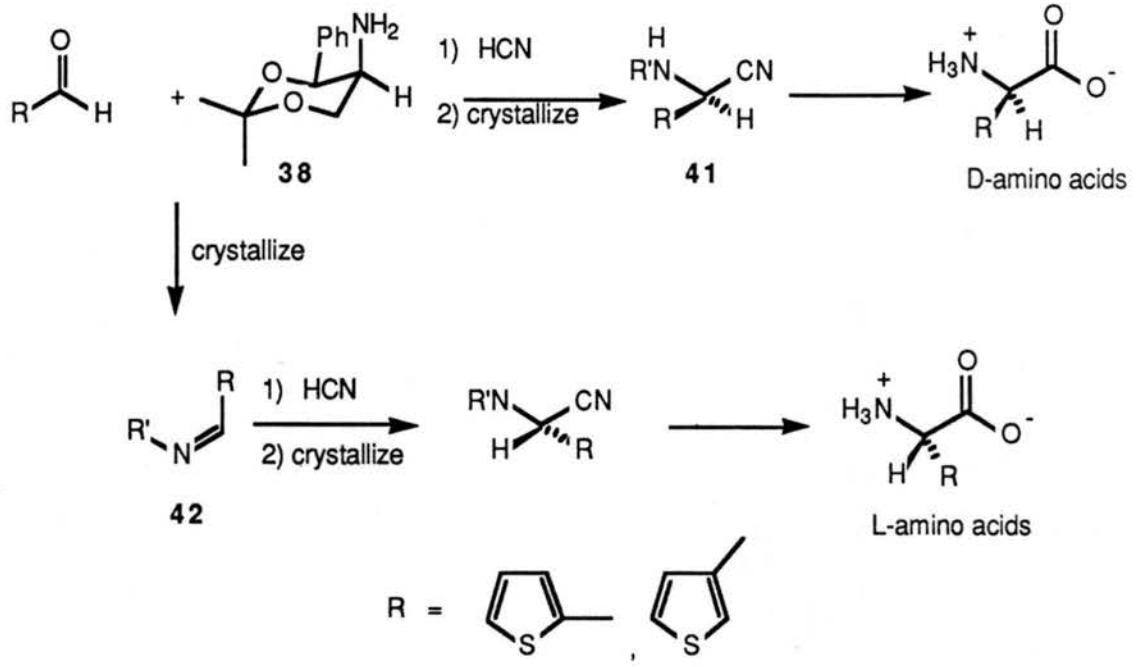
An interesting asymmetric Strecker synthesis has been developed by Weinges and coworkers using (4S,5S)-(+)-4-amino-2,2-dimethyl-4-phenyl-1,3-dioxane **38** as the chiral auxiliary. Condensation of **38** with benzaldehyde (or 4-methoxybenzaldehyde) and HCN gives the corresponding aminonitrile **39** as approximately a 7:3 mixture of diastereomers. Crystallization gives the major product diastereomerically pure. Hydrolysis of the nitrile occurs with concomitant opening of the dioxane moiety to give, after cyclization, the tetrahydro 1,4-oxazine-2-one **40**. Ring opening followed by oxidative deprotection with sodium periodate gives the enantiomerically pure amino acid (Scheme 15).[22]

SCHEME 15



Working with the same chiral amine, Weinges found that the enantioselectivity can be reversed by crystallization of the intermediate imine. Treatment of **38** with a thiophene carbaldehyde in the presence of HCN gave the corresponding aminonitrile **41**. Crystallization followed by deprotection (hydrolysis, periodate oxidation) gave the enantiomerically pure D-α-amino acids. If the intermediate imine **42** is crystallized and then treated with HCN, the diastereomeric amino nitriles crystallize giving enantiomerically pure L-amino acids upon hydrolysis (Scheme 16).[23] The diastereoselectivity of the asymmetric Strecker reaction is not great but crystallization allows for the preparation of amino acids in high enantiomeric excess.

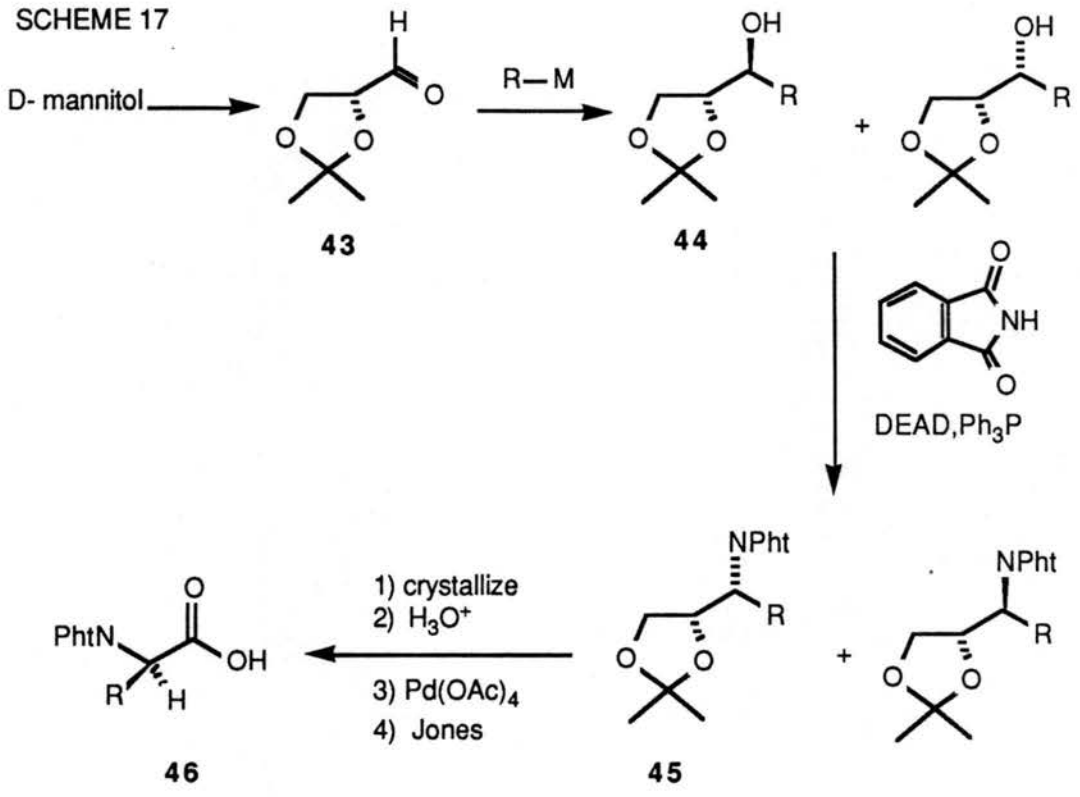
SCHEME 16



Selective Syntheses of D-Amino Acids

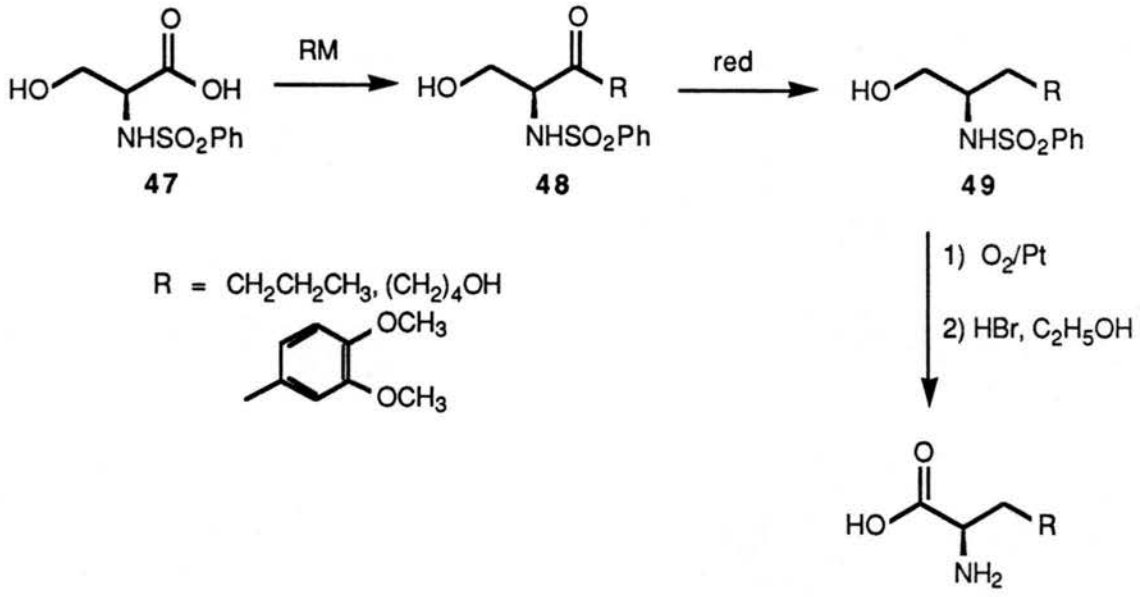
The D antipode of α-amino acids generally is not found in nature. Because of the considerable biological interest in these compounds their preparation has received much attention. One synthesis uses β-mannitol as the chiral educt. This route takes advantage of the facile addition of organometallic reagents to the aldehyde group of R-2,3-isopropylideneglyceraldehyde **43** which is readily obtained from β-mannitol. The coupling takes place with 50-80% diastereoselectivity to give the protected triol **44**. Treatment of the mixture with phthalimide under Mitsunobu conditions affords the phthalimidodiol **45**. The syn isomer is isolated from this mixture by crystallization. Removal of the acetonide, glycol cleavage, and oxidation yields the N-protected-D-amino acid **46** in 94-97% enantiomeric excess (Scheme 17).[24]

SCHEME 17



Rapoport has developed an efficient synthesis of D-amino acids using L-serine as the chiral educt. The N-(phenylsulfonyl)-L-serine **47** aminoacylates several types of organometallic compounds to give the corresponding ketone **48**. Reduction of the carbonyl gives the primary alcohol **49** which is then oxidized and deprotected to furnish the enantiomerically pure D amino acid (Scheme 18).[25]

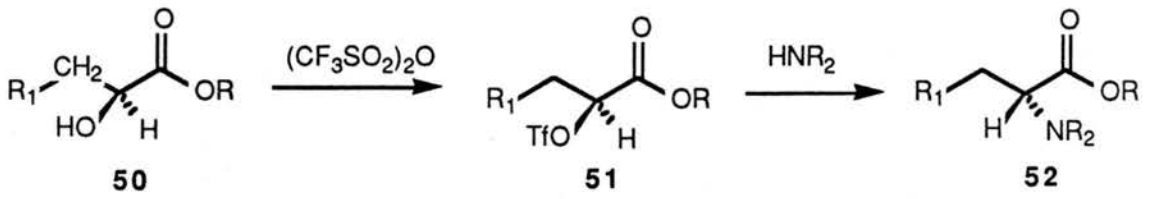
SCHEME 18



Nucleophilic Amination

Nucleophilic amination has not been widely exploited in the enantioselective synthesis of amino acids. The sequence can be plagued by the undesired side reactions of racemization and elimination. Nevertheless, researchers have addressed the problem with some degree of success. In 1983 Effenberger and coworkers reported the synthesis of optically active α-amino acids from the corresponding α-hydroxy carboxylic acids **50**. The hydroxy group is activated towards nucleophilic displacement as the trifluoromethane sulfonate ester **51**. Substitution with an amine takes place with complete Walden inversion to give the amino acid derivative **52** of opposite stereochemistry in high e.e. (Scheme 19).[26] This method provides a facile route to N-substituted α-amino acids. The preparation of the optically active α-hydroxy carboxylic acids was not examined.

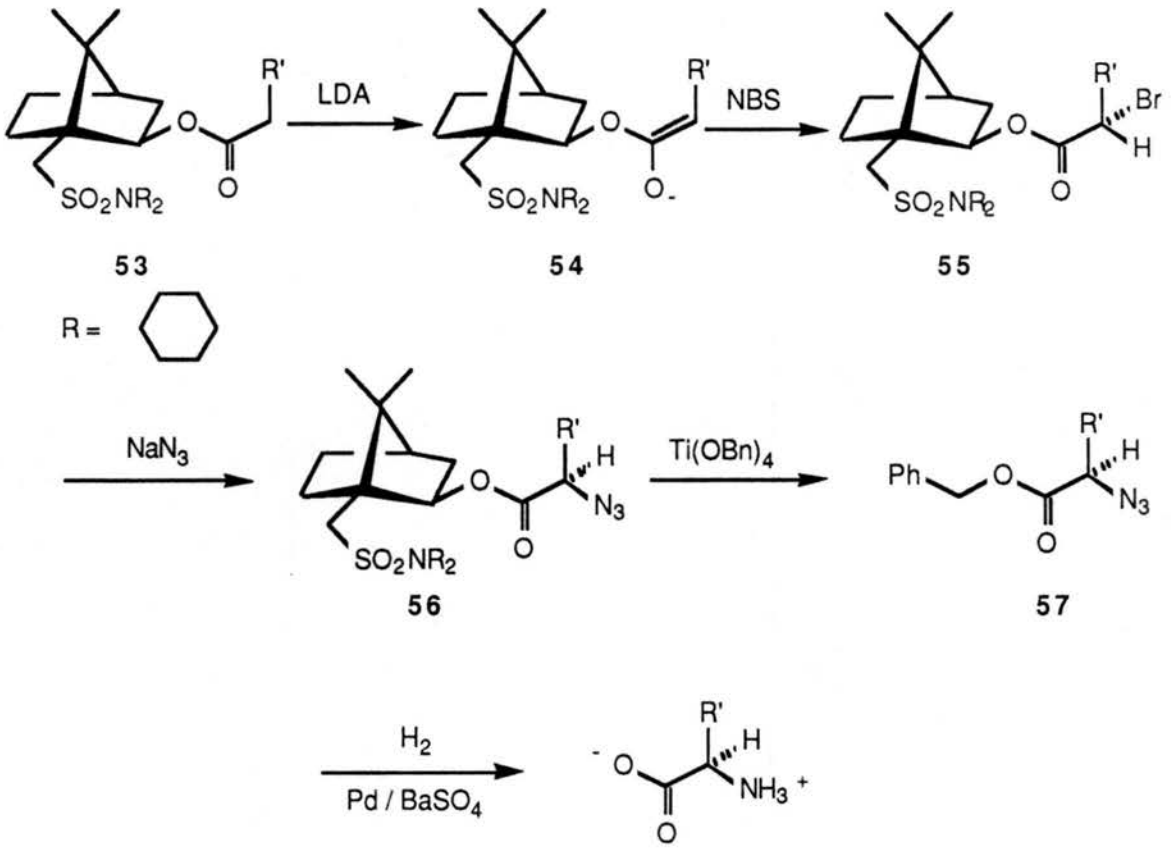
SCHEME 19



50 **51** **52**

An enantioselective nucleophilic amination that exploits the simple and efficient π-face selective bromination of lithium enolates of 1-sulfonamido-isobornyl esters **54** has been developed by Oppolzer. Treatment of ester **53** with LDA furnishes the enolate **54**. Addition of NBS results in the formation of bromide **55** which is obtained in ≥94-99% diastereomeric purity after crystallization. Nucleophilic displacement of the bromide by sodium azide gives the corresponding azide **56**. Crystallization and transesterification with $Ti(OCH_2C_6H_5)_4$ furnishes the benzyl ester **57**. Catalytic hydrogenation reduces the azide moiety and cleaves the benzyl ester to give the desired amino acid Zwitterion (Scheme 20). A variety of amino acids have been prepared by this route in good overall yield (72-87%) and high enantiomeric excess (93.8-98.0%).[27]

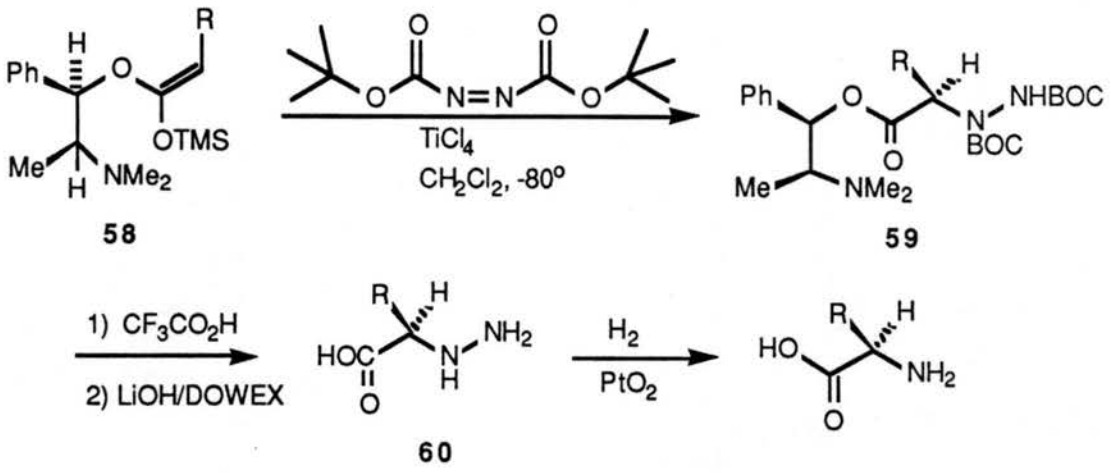
SCHEME 20



Electrophilic Amination

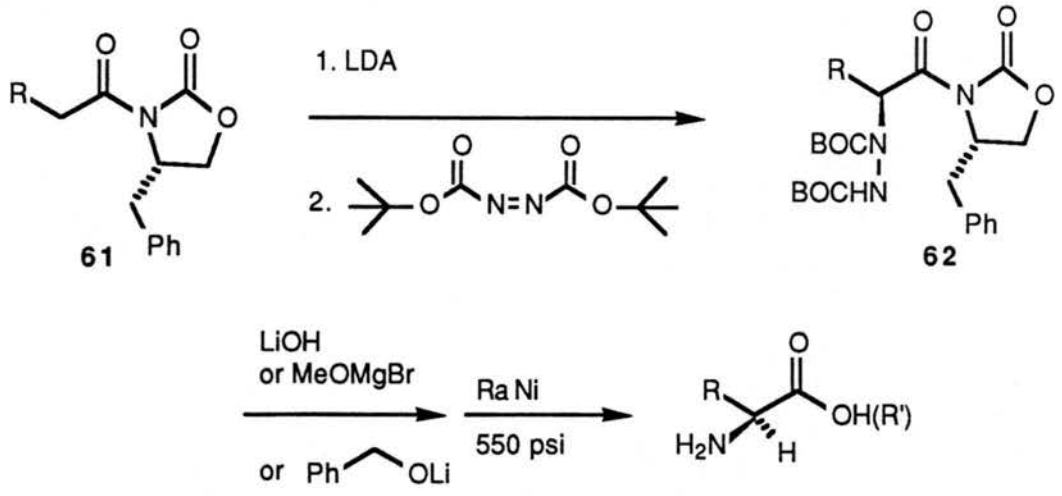
Four groups have developed routes to optically active amino acids by addition of an electrophilic amine source to a chiral enol(ate). Gennari and coworkers have devised a $TiCl_4$ mediated coupling of the E-silyl ketene acetals of (1R,2S)-N-methylephedrine esters **58** with di-t-butyl azodicarboxylate to give derivative **59** in 45-70% yield. Treatment with acid to remove the t-BOC groups followed by base hydrolysis affords the hydrazino acids **60**. Catalytic reduction gives the amino acids, obtained in 78-91% e.e. (Scheme 21).[28a] The enantiomeric excess can be increased to ≥98% by recrystallization of intermediate **60**.

SCHEME 21

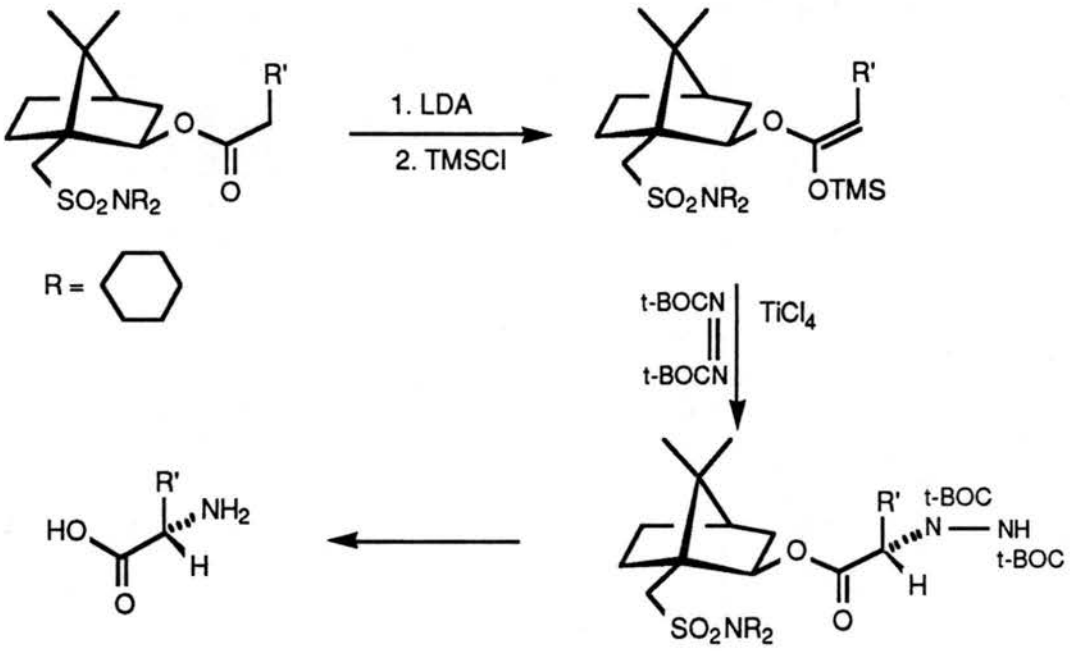


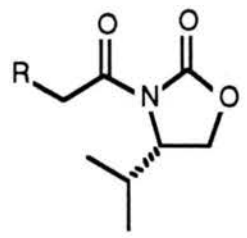
Evans and coworkers, pioneers in the stereoselective alkylation of the enolates of chiral N-acyl oxazolidones **61**, have simultaneously reported similar methodology in the synthesis of amino acids. Generation of the enolate with LDA followed by addition of di-t-butyl azodicarboxylate results in formation of the t-BOC protected hydrazino ester **62** in good yield (91-96%) and high diastereomeric excess (94-99%). Transesterification or hydrolysis removes the oxazolidone moiety. Treatment with acid cleaves the t-BOC protecting groups and hydrogenation furnishes the amino acid (ester) (Scheme 22).[28b] Trimble and Vederas independently developed the same methodology using the chiral N-acyl oxazolidone derived from L-valinol **63**.[28c] Oppolzer also independently reported a similar approach using a camphor - derived chiral auxilliary (Scheme 22b).[28d]

SCHEME 22a



SCHEME 22b



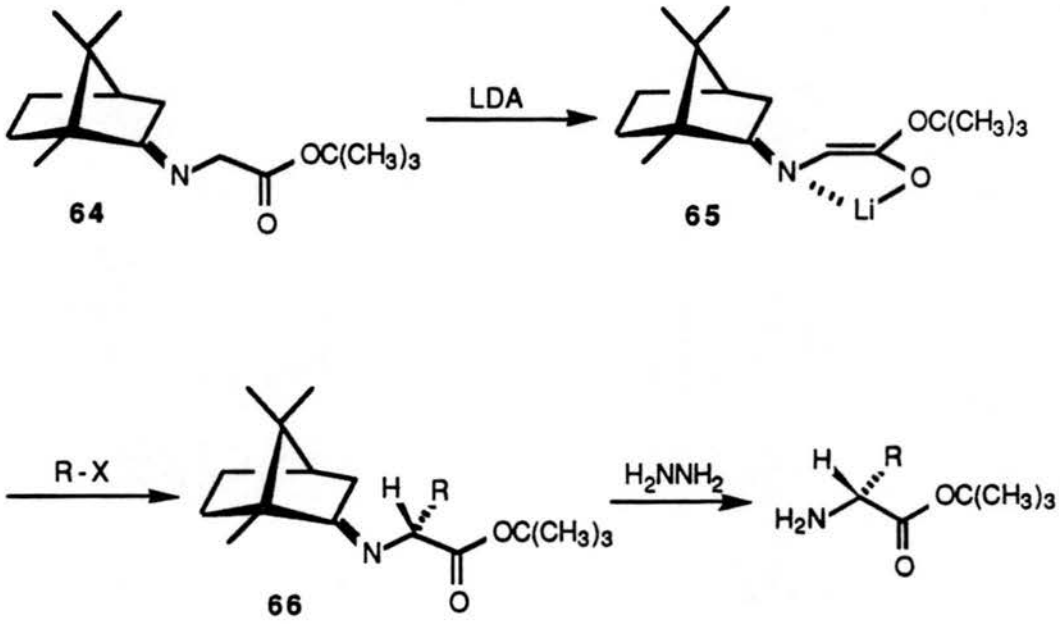


63

Chiral Glycine Enolates

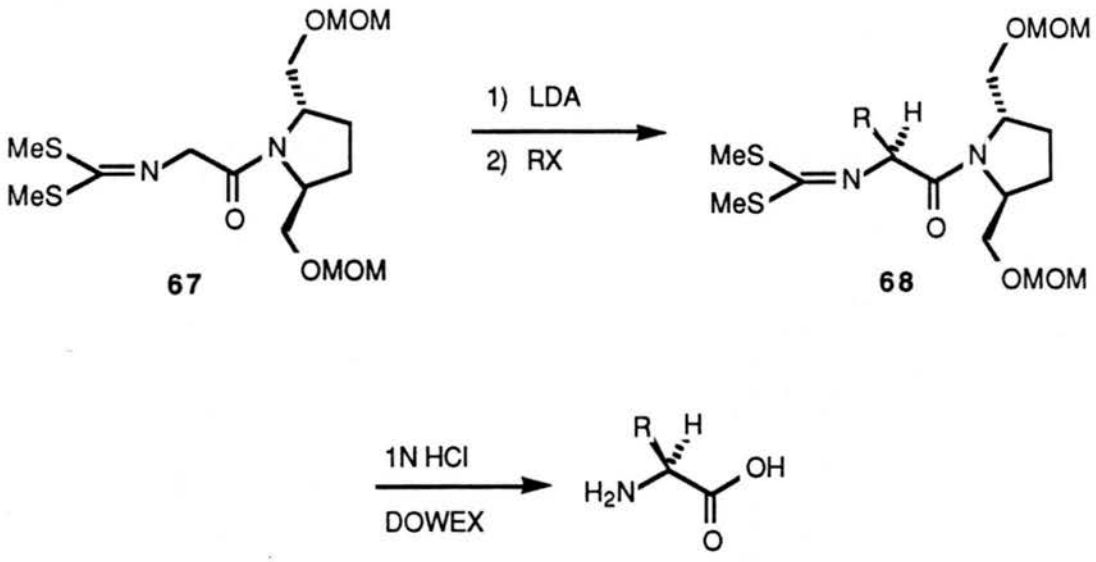
There has been a great deal of effort involved in the development of chiral glycine enolates as amino acid precursors. The syntheses utilize either acyclic glycine imino esters containing a chiral auxiliary or chiral heterocycles possessing a glycine residue within the ring. McIntosh and coworkers have examined the (R) camphor derived imine of t-butyl glycine **64**. Deprotonation with LDA gives enolate **65**. Addition of an alkyl halide results in alkylation taking place preferentially from the Re face of the enolate to give the corresponding R amino acid ester imine **66** (Scheme 23).[29] Simple alkyl halides larger than methyl couple with de's of approximately 50%. With allylic and benzylic halides the d.e.'s ranged from 75-99%. Hydrolysis of the camphor imine **66** appears to be exceedingly difficult. Only the phenylalanine derivative (R = Bn) has been hydrolyzed using hydroxylamine.

SCHEME 23



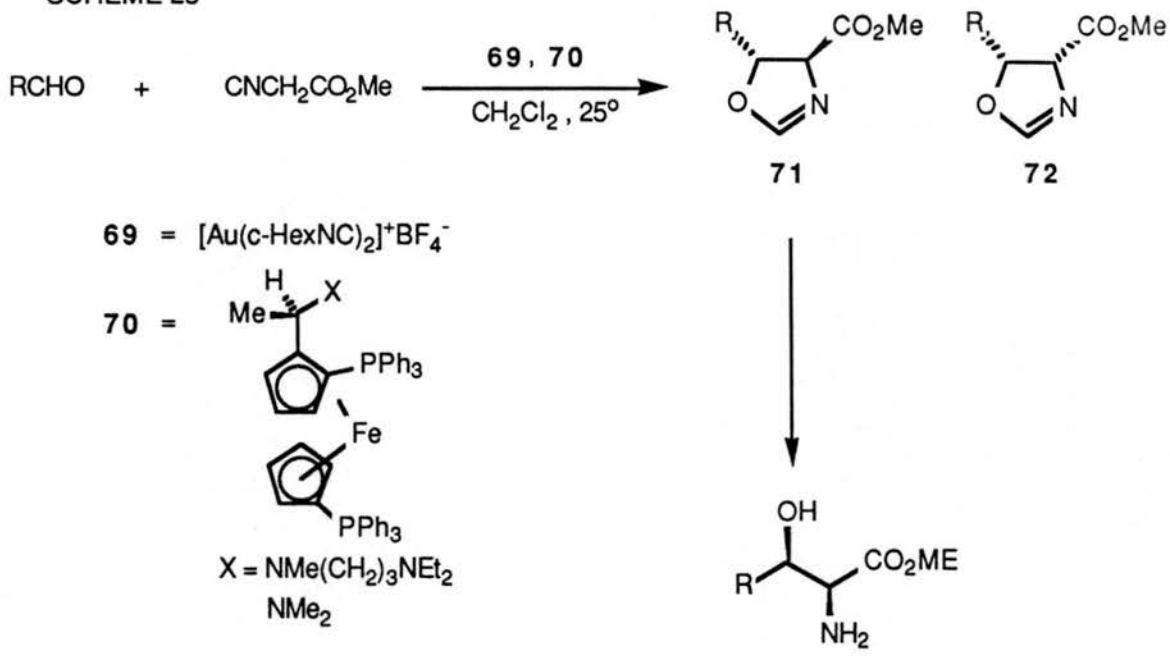
A second acyclic chiral glycine enolate was prepared from the (S,S)-2,5-bis-methoxymethyl pyrrolidine amide of glycine protected as the bis-methylthioimine (**67**). Enolate formation (LDA/THF/-78°C) and addition of an alkyl halide or alkyltriflate gives the derivatized amide **68**. The free amino acid is obtained upon acid hydrolysis and ion exchange chromatography. Several amino acids were prepared with e.e.s ranging from 81-97% (Scheme 24).[30]

SCHEME 24



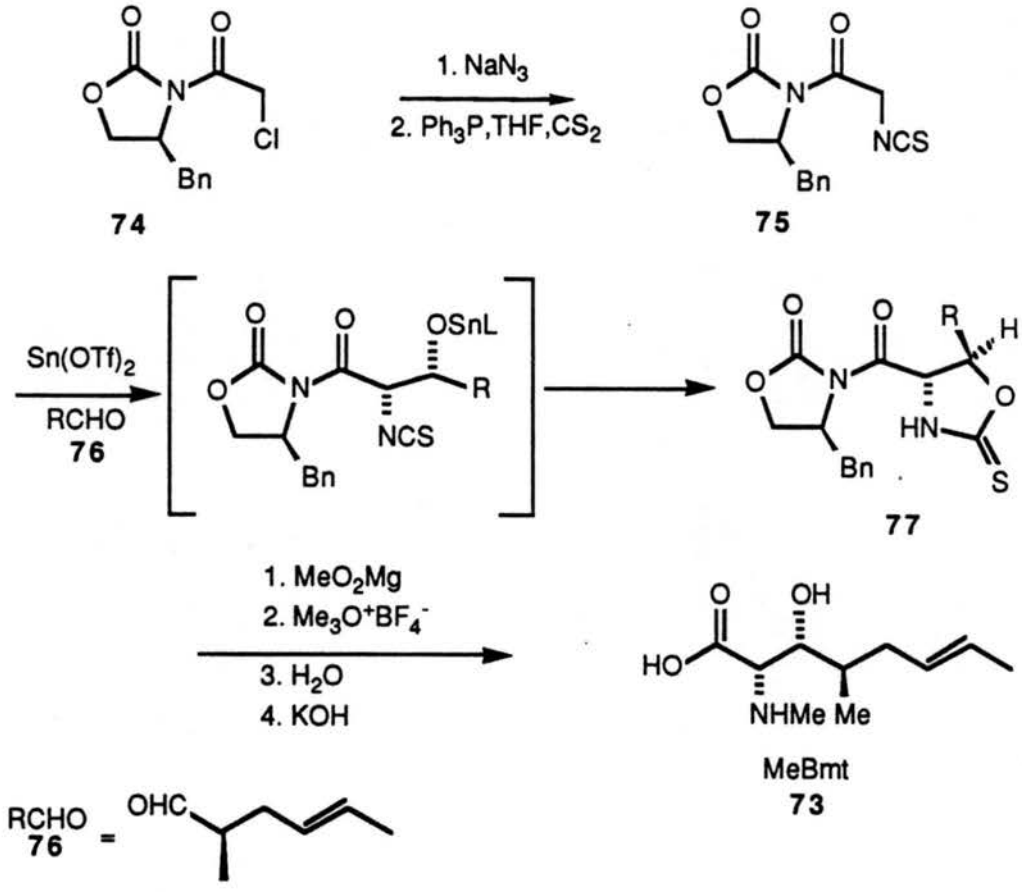
A novel β-hydroxy-α-amino acid synthesis has been devised that utilizes an isocyanoacetate as a glycine enolate equivalent. Ito and collaborators have found that a variety of aldehydes will undergo a stereoselective aldol condensation with a cyanoacetate when catalyzed by a chiral ferrocenylphosphine-Gold(I) complex. Thus, treatment of an aldehyde with methyl isocyanoacetate in the presence of bis(cyclohexylisocyanide) gold(I) tetrafluoroborate **69** and (R)-N-methyl-N-[2-(dialkylamino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl amine **70** gives the corresponding oxazolines **71**, **72** in high yields (Scheme 25).[31] The trans isomer **71** always predominates and is formed in 72-97% e.e. Hydrolysis of the oxazoline (1N HCl, MeOH) affords the β-hydroxy-α-amino acid ester hydrochloride.

SCHEME 25



Using aldol methodology, Evans and coworkers have prepared the unusual amino acid MeBmt **73**. This compound is a constituent of the important immunosuppressive cyclic peptide cyclosporin, and appears to be essential to the biological activity of this chemotherapeutic agent. The Evans synthesis of MeBmt utilized the chiral isothiocyanate **75**, derived from chloroacetate **74**, as a glycine enolate synthon. It was found that aldehyde **76** undergoes a stannous triflate mediated aldol condensation with **75** to afford adduct **77** enantiomerically pure and in 73% yield (Scheme 26).[32] Transesterification, N-methylation, and hydrolysis furnished the desired compound which was identical to authentic MeBmt. This synthesis should allow the ready preparation of a variety of MeBmt analogs and thereby facilitate structure-activity relationship studies.

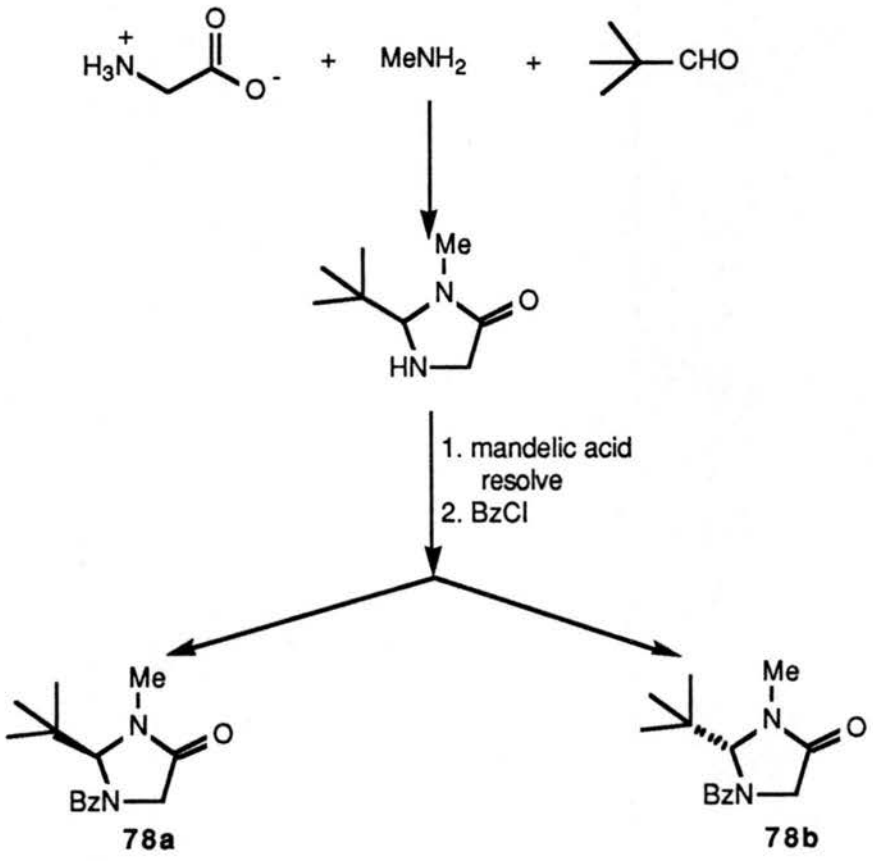
SCHEME 26



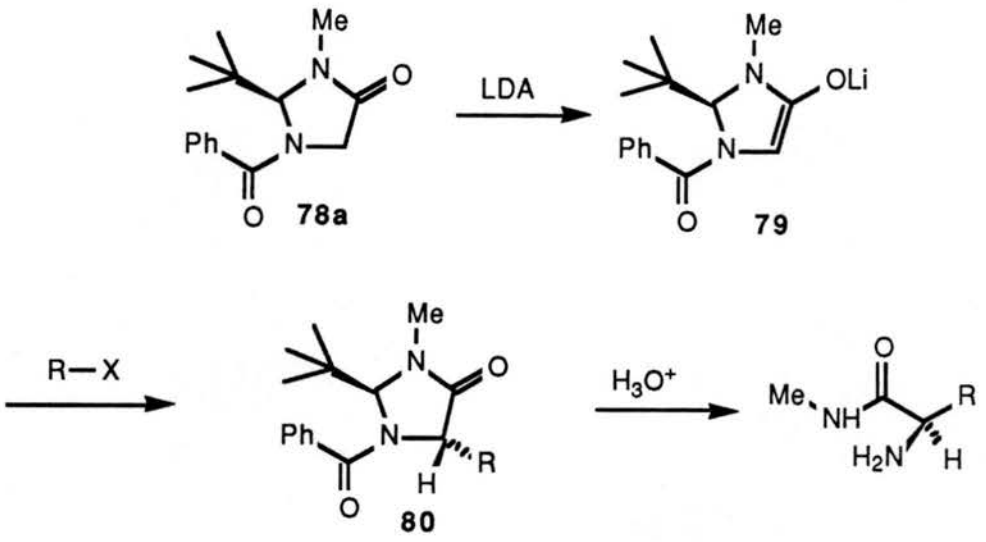
Two particularly noteworthy chiral glycine enolates have been developed based on heterocyclic systems containing a stereogenic center that directs alkylation. Seebach and coworkers have prepared the imidazolidinones **78a,b** by multistep syntheses involving the side chain degradation of the chiral imidazolidinones obtained upon condensation of pivalaldehyde with methionine or O-benzylserine. A much more efficient route to **78a** and **78b** was developed and relies on the resolution of the diastereomeric mandelate salts of racemic **78**. The racemic compound is easily obtained by condensation of methylamine, glycine, and pivalaldehyde (Scheme 27).[33] The lithium enolate **79** is formed upon treatment with LDA. Alkylation and hydroxyalkylation occurs trans to the t-butyl group to give the homologated heterocycle **80** with good (86->95%) diastereoselectivity.

Deprotection to the free amino acid appears to be difficult. The simple alkyl derivatives are hydrolyzed to give the corresponding N-methyl amides (Scheme 28).[34] The hydroxy alkylated derivatives can be cleaved to the free amino acids by refluxing in 6N HCl. It has been suggested[34] that this more facile deprotection might be due to anchimeric assistance (Scheme 29).

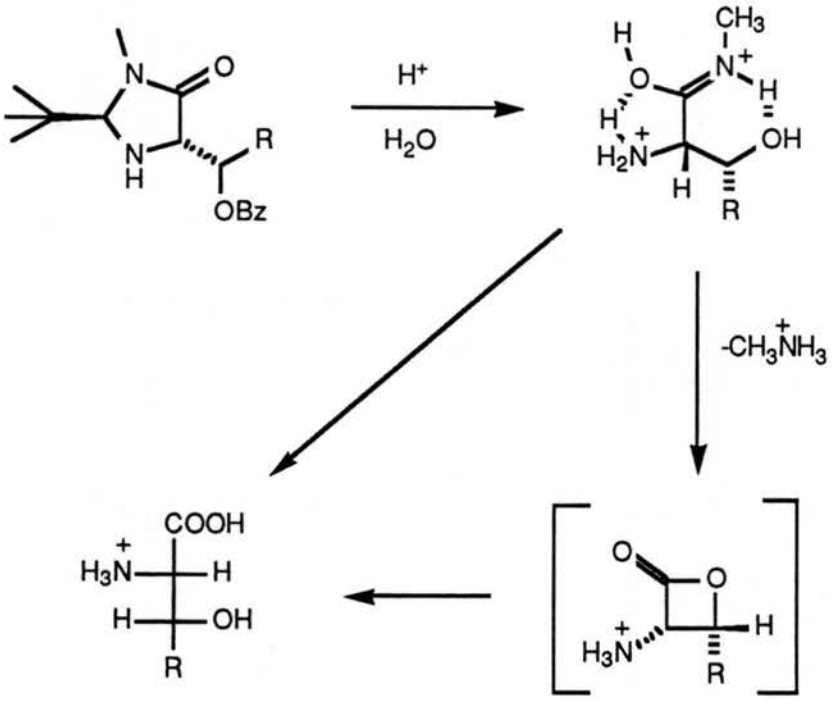
SCHEME 27



SCHEME 28



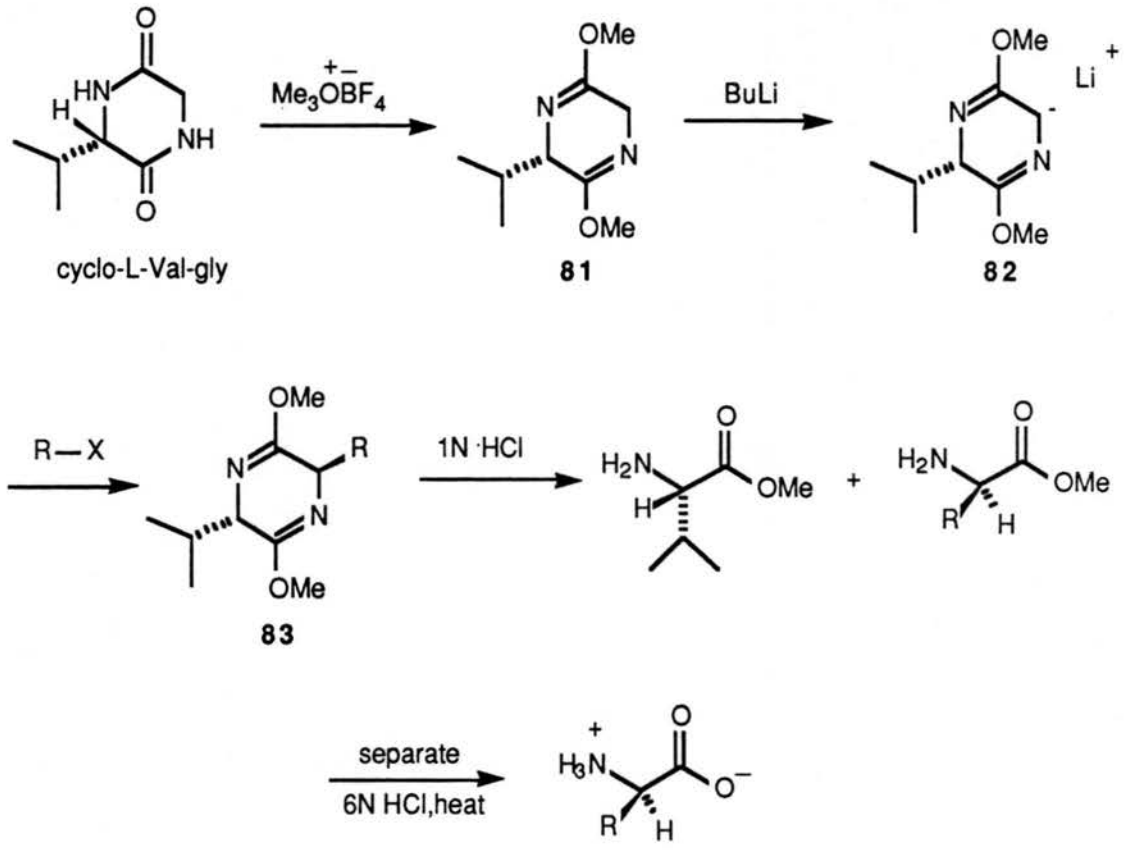
SCHEME 29



One of the most general α-amino acid syntheses developed to date is that devised by Schöllkopf. His method employs the bis lactam ether of the cyclic dipeptide cyclo-L-

Val-Gly **81**. The heterocycle undergoes metallation upon treatment with butyllithium. Alkylation and hydroxyalkylation takes place smoothly to give the homologated heterocycle **83** in good yields with uniformly high diastereoselectivity. Mild acid hydrolysis (1N HCl) affords a mixture of the two amino acid esters which are then separated. More forcing hydrolysis conditions (6N HCl, heat) gives the free amino acid (Scheme 30).[35] This methodology has been employed to synthesize a wide variety of amino acids (esters) in high enantiomeric excess.

SCHEME 30

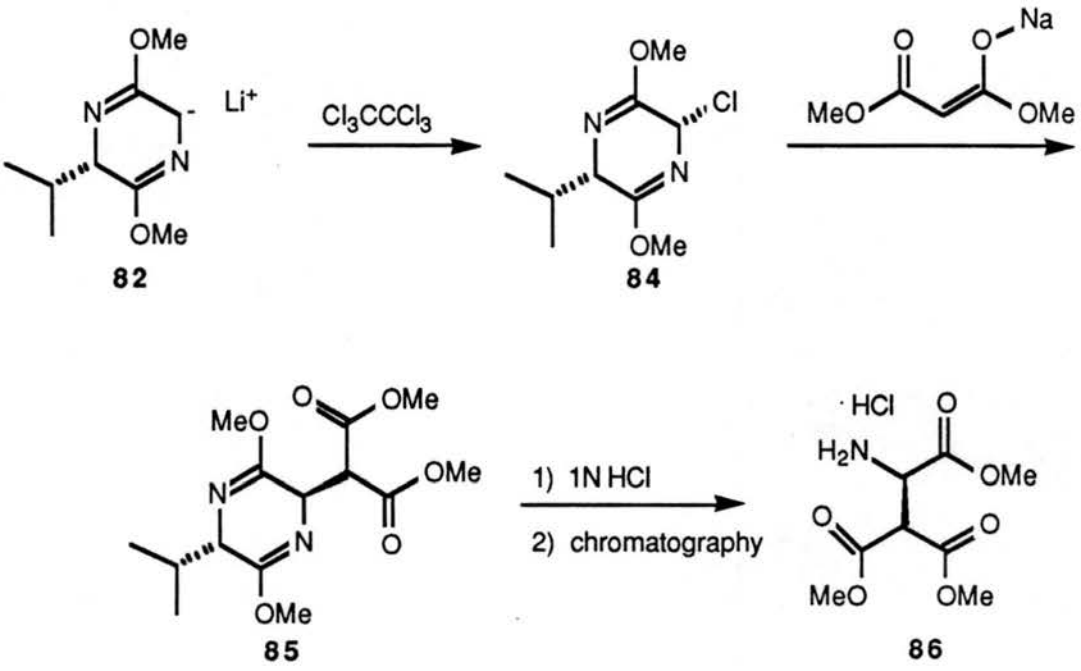


Electrophilic Glycinates

While not as widely exploited as glycine enolates, electrophilic glycinates have been employed as precursors to chiral, non-racemic amino acids. Schollkopf reported that the metallated bis lactim ether **82** is chlorinated upon addition of hexachloroethane. The resulting chloride **84** is obtained as a 94:6 ratio of diasteroemers with the cis compound

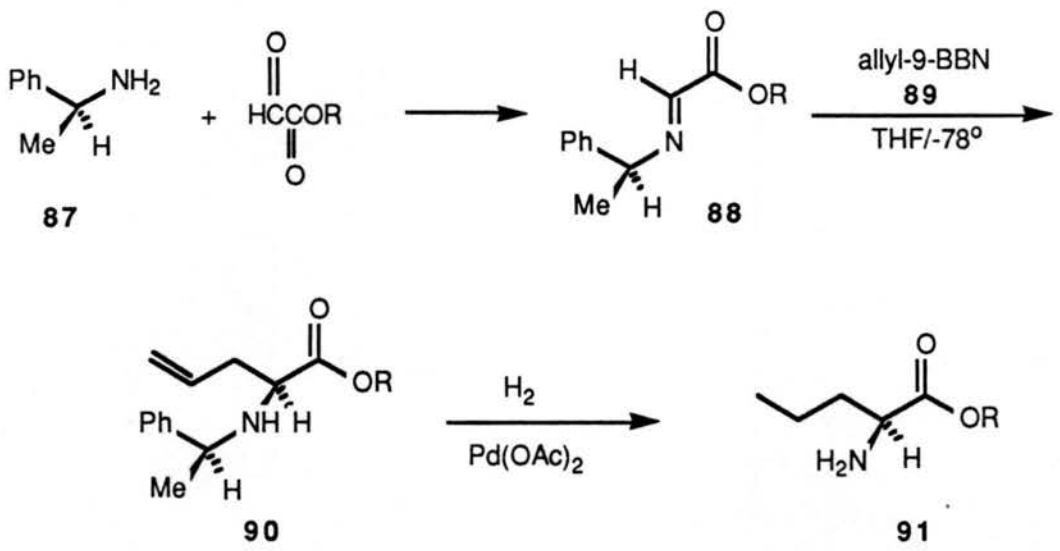
predominating. Chloride **84** reacts with a variety of "soft" nucleophiles (borohydrides, thiolates, resonance stabilized anions) to give the homologated derivatives with inversion of configuration of the new stereogenic center. Condensation of the sodium enolate of dimethyl malonate with **84** followed by hydrolysis and chromatography furnished the trimethylester of (R)-β-4-carboxyaspartic acid **86** in 72% yield (Scheme 31).[36]

SCHEME 31

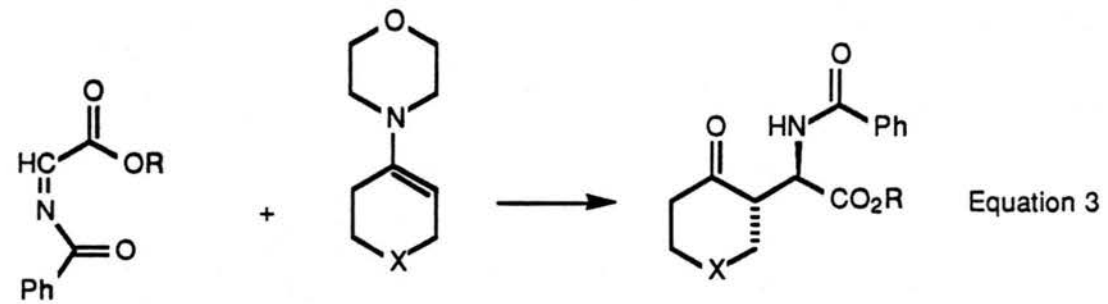


Several groups have developed chiral α-imino esters as amino acid precursors. Yamamoto found that the chiral α-imino acid **88** bearing the chirality center adjacent to the nitrogen will undergo stereoselective coupling with allylic boron compounds. Imino ester **88** is prepared by condensation of (S)-(-)-α-methyl benzyl amine **87** with a glyoxylate ester. Addition of allyl 9-borabicyclo[3.3.1]nonan-9-yl **89** to **87** at -78°C in THF resulted in formation of the allyl glycine derivative **90** obtained in 92% yield and 92% enantiomeric excess. Hydrogenolysis removed the benzyl group affording the corresponding norvaline ester **91** (Scheme 32).[37]

SCHEME 32



Steglich has found that imino esters **92** react with cyclic enamines **93** to give the (racemic) cyclic amino acid derivative **94** with >95% diastereoselectivity favoring the anti compound. In an effort to prepare enantiomerically pure amino acids the reaction was carried out using the (-)-menthyl and (-)-8-phenylmenthyl imino esters **92b,c**. The diastereoselectivity was still high but the enantioselectivity was low (27 and 67% respectively) (Equation 3). When a second chiral auxiliary was added, this time in the enamine, the enantioselectivity increased considerably. Thus treatment of imino ester **95** with enamine **96** gave the cyclic amino acid derivative **97** in ≥99% de and ≥99% ee (Equation 4).[38]

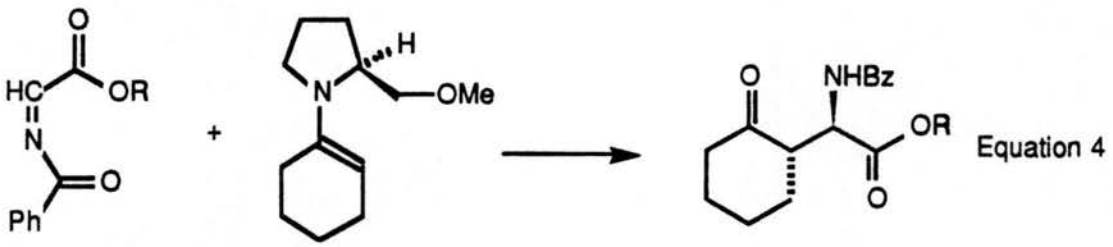


92 93 94 X = CH_2, S

Equation 3

	de	ee
a	>95	–
b	>95	27
c	>95	67

a = CH_3
b = (-)mentyl
c = (-)-γ -phenylmentyl



95 96 97

Equation 4

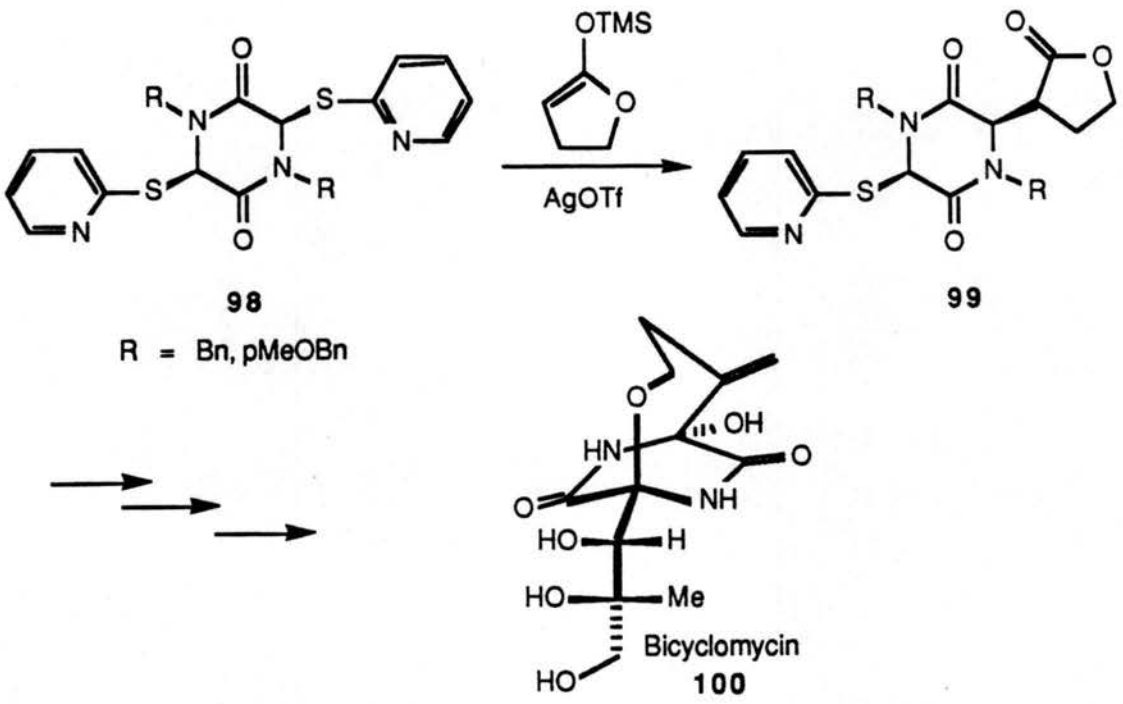
R = (+)menthyl R = (+)menthyl

The preceding survey, given in order to demonstrate the intense effort being expended in the area of enantioselective amino acid synthesis, is necessarily brief. In most cases, the factors controlling the stereoselectivity are not discussed. While several efficient and general routes to these compounds have been reported (particularly the enolate chemistry of Schollkopf, Seebach, Oppolzer, and Evans) there is still a need for complementary methodology. The ideal synthesis would allow facile preparation of a wide variety of amino acids in uniformly high enantiomeric excess. The final product obtained should be the amino acid zwitterion since hydrolysis of amino acid esters often occurs with attendant racemization. Also, the final deprotection to give the amino acid should require minimal purification. We undertook the development of a general enantioselective synthesis of α-amino acids based on a heterocyclic containing a latent electrophilic glycine equivalent.

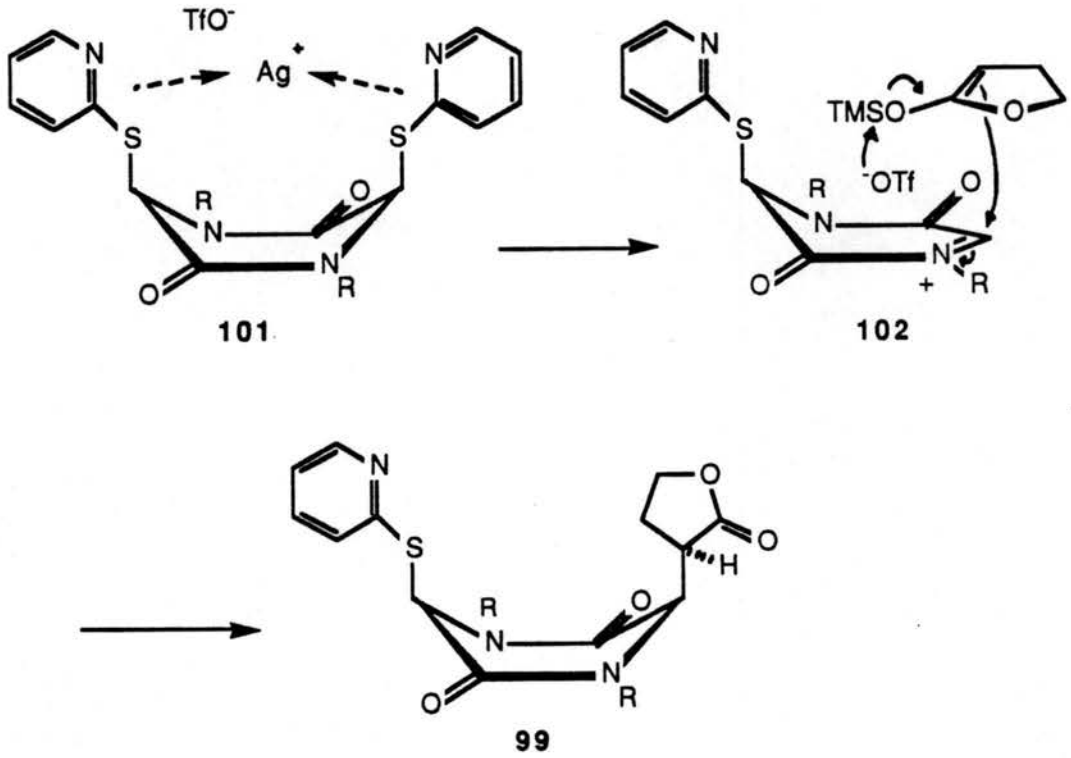
D. Electrophilic Piperazinediones

During the development of the total synthesis of the unique dipeptide antibiotic bicyclomycin **100**, Armstrong and Williams demonstrated the utility of a novel carbon-carbon bond forming reaction. This method involved the Lewis acid mediated coupling of silyl ketene acetals with activated piperazinediones **98**. The coupling takes place with chemoselective monosubstitution in a stereoselective manner to afford the syn diastereomer **99** as the major product (Scheme 33).[39] Presumably the new bond forming reaction proceeds as follows: the complex **101** is obtained upon addition of a Lewis acid to the piperazinedione. The silyl ketene acetal then undergoes electrophilic attack by the presumed iminium ion **102**, giving rise to product (Scheme 34). The resultant piperazinedione **99** now contains one amino acid residue newly functionalized in the α-position by an electrophilic substitution reaction. It was desirable to extend this methodology to develop a general enantioselective synthesis based on these types of electrophilic glycinates. A chiral tetrahydro 1,4-oxazine-2-one **103** was initially envisioned as the amino acid precursor. It was proposed that the heterocycle could be activated in the 3-position as the pyridyl thioether **104** and coupled with a silyl ketene acetal stereoselectively. Deprotection would then give the corresponding β-carboxy amino acid **106** (Scheme 35). Two tetrahydro-1,4-oxazin-2-ones, **107** and **108**, have been prepared and examined as α-amino acid precursors. The results of these studies are presented in the ensuing chapters.

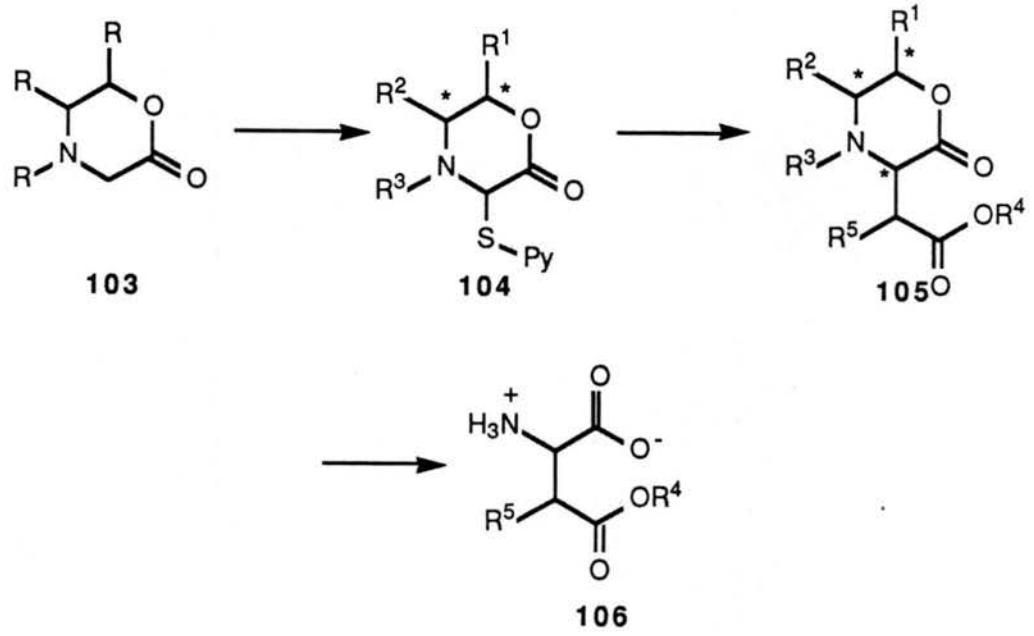
SCHEME 33

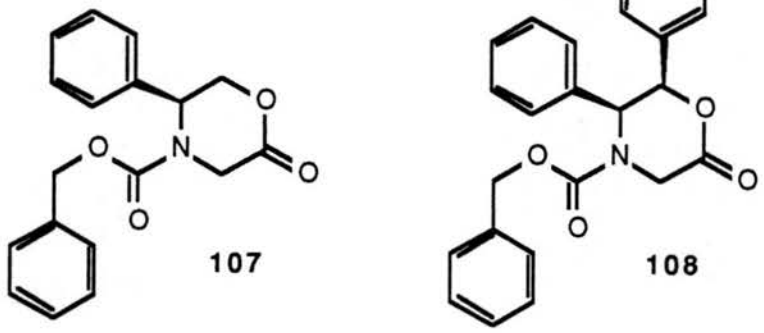


SCHEME 34



SCHEME 35


R
R
N
R
O
O
103
R1
R2
R3
N
O
O
S
Py
104
R1
R2
O
N
R3
O
R5
OR4
O
105
+
H3N
O
O-
R5
OR4
O
106

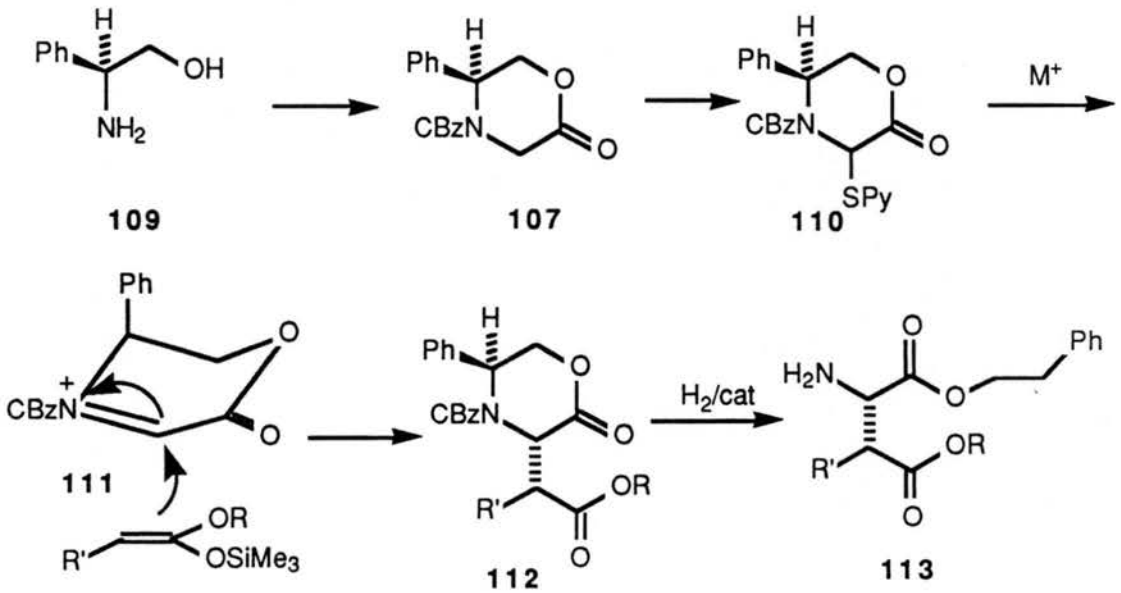

O
N
O
O
O
107
O
N
O
O
O
108

CHAPTER II

(5S)-4-BENZYLOXYCARBONYL-5-PHENYL-2,3,5,6-TETRAHYDRO-1,4-OXAZINE-2-ONE AS AN AMINO ACID TEMPLATE

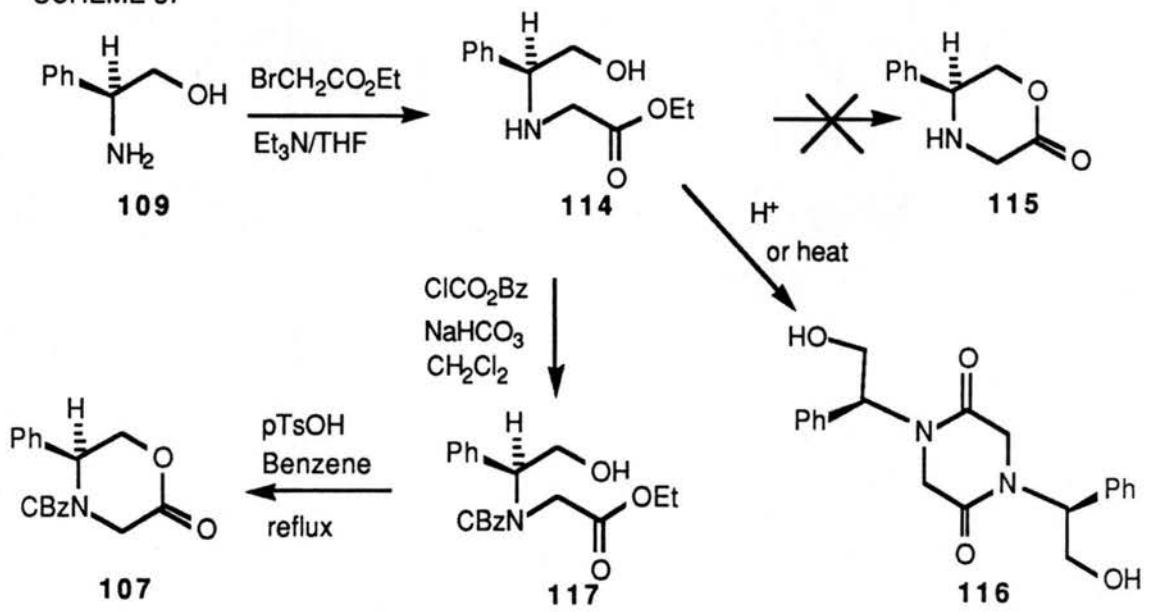
The amino acid template examined first was (5S)-4-benzyloxycarbonyl-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazine-2-one **107**. (S)-(-)-Phenyl glycinol **109** was the source of the requisite stereogenic center. Upon preparation of the heterocycle and activation of the 3-position as the pyridyl thioether **110**, coupling was to be effected as with the piperazinediones. It was anticipated that any stereoselectivity observed during coupling would arise from preferential attack of the putative imminium ion **111** on the silyl ketene acetal from the least hindered face of the ring. Once obtained, the homologated heterocycle **112** would be deprotected via hydrogenation. These conditions would be expected to remove the benzyloxy carbonyl (CBz) moiety and cleave the benzylic carbon-nitrogen bond to afford the amino acid as the corresponding phenethylester as shown in Scheme 36.

SCHEME 36



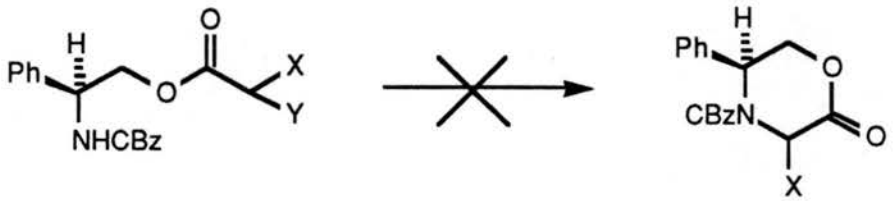
The synthesis of the 1,4-oxazinone required simply the addition of a two carbon fragment to phenylglycinol. Condensation of the phenylglycinol with ethylbromoacetate gave amino ester **114**. Unfortunately, direct cyclization to the heterocycle **115** failed, giving only the N,N-dialkyl piperazinedione **116**. Treating **114** with benzylchloroformate under Schotten-Baumann conditions furnished the N-benzyloxycarbonyl derivative **117**. Acid catalyzed cyclization could now be effected by refluxing in benzene with azeotropic removal of ethanol to afford the desired oxazinone **107** (Scheme 37).

SCHEME 37



Activation of the heterocycle **107** towards substitution was now necessary. In the piperazinedione series only those compounds activated as the pyridylthioethers underwent facile coupling; thus, it appeared to be of primary importance to incorporate this moiety into the oxazinone. Electrophilic glycinate **110** was to be prepared by generation of the lithium enolate followed by addition of dipyridyl disulfide (Equation 5). Unfortunately, all attempts to effect this conversion failed. It has since become apparent that, in general, N-benzyloxycarbonyl-tetrahydro-1,4-oxazin-2-ones are unstable to basic conditions. An alternate route to **107**, developed earlier, involved the low yield cyclization of an α

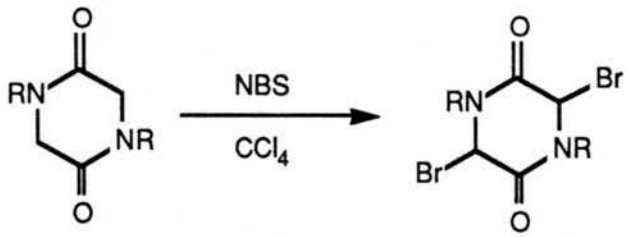
bromoester. It was believed this methodology held some potential for the preparation of an oxazinone already activated in the 3-position (Equation 6). A number of α-substituted and α-disubstituted esters were prepared. Cyclizations of these compounds were unsuccessful (Table 1).



Equation 6

X,Y=ClCl
SPy,SPy
OMe,OMe

It is known that piperazine-2,5-diones can be oxidized to the corresponding 3,6-dibromo compound by treatment with NBS in CCl_4 (Equation 7).[40] Preliminary attempts

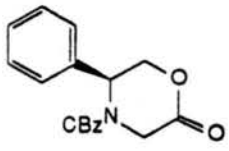
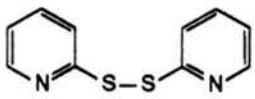
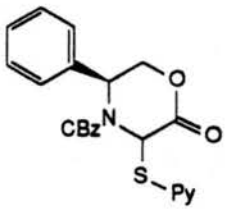
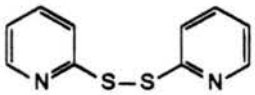
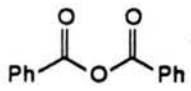
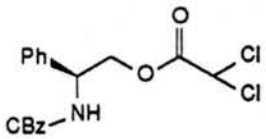
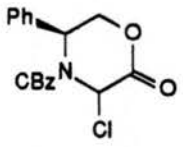
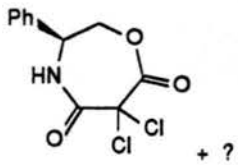
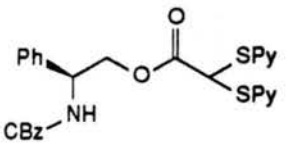
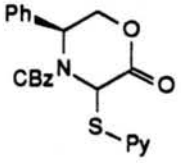
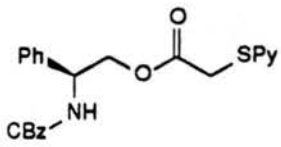


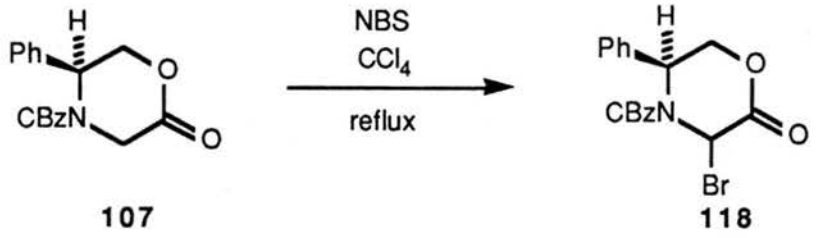
Equation 7

R = Bn,p-OMeBn

at bromination of the heterocycle using **107** as an oil proved fruitless. However, it was observed while using crystalline **107** that the compound is not readily soluble in hot CCl_4 but dissolution can be achieved by maintaining the mixture at reflux for 15 to 20 minutes. Upon addition of NBS to the refluxing solution bromination readily takes place to afford, after cooling, filtering and concentrating, bromide **118** as a clear, colorless oil (Equation 8). The activated heterocycle proved to be somewhat unstable, and attempts at purification by silica gel chromatography or by recrystallization lead only to extensive decomposition. Fortunately, purification proved unnecessary as the crude bromide could be used directly.

TABLE I

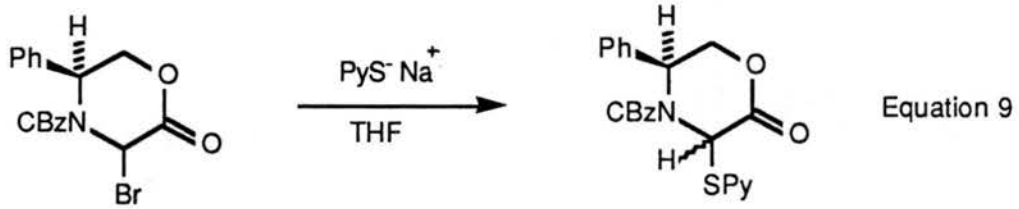
SUBSTRATE	CONDITIONS	DESIRED PRODUCT	OBTAINED
	LDA 		—
	 AIBN	"	SM
	Solution 		
	NaH, THF		 + ?
	pTsOH CH_2Cl_2		SM
	AgOTf, THF	"	SM
	AfOTf, THF	"	SM
	MeI, DMF	"	SM
	NCS, CCl_4 $ClCH_2CH_2Cl$	"	SM



107 **118**

Equation 8

Displacement of the halide of **118** by the sodium salt of 2-mercaptopyridine gave the pyridyl thioether **110** in 66% yield as a mixture of diastereomers (Equation 9). This derivative was stable to chromatography but isolation of the individual diastereomers proved impossible due to facile epimerization at C3. As the coupling mechanism was expected to proceed through imminium ion **111** the occurrence of the diastereomeric mixture was not deemed a problem.

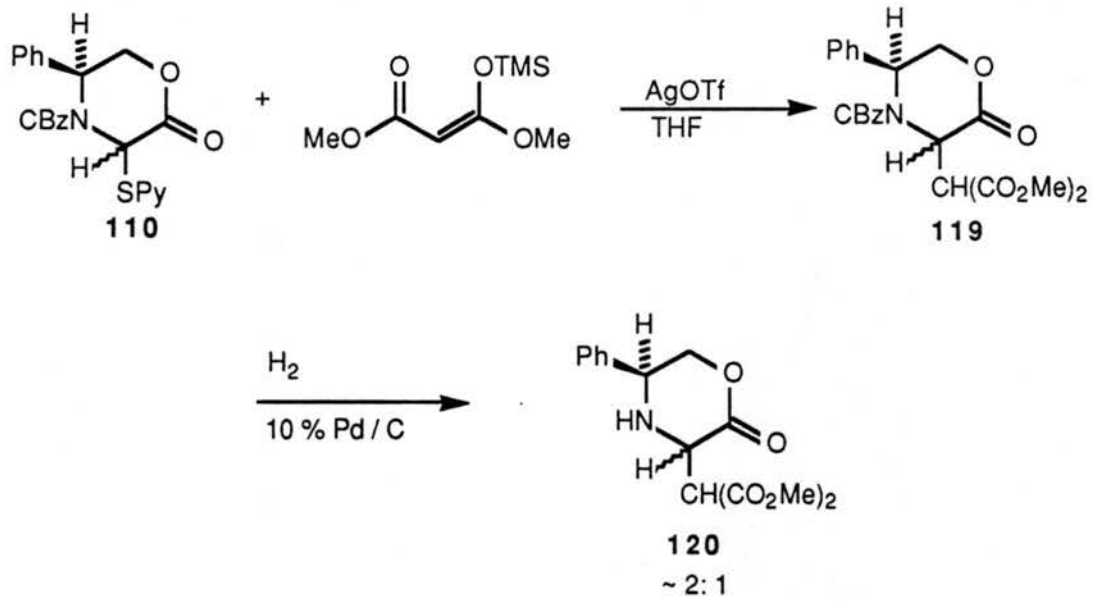


118 **110**

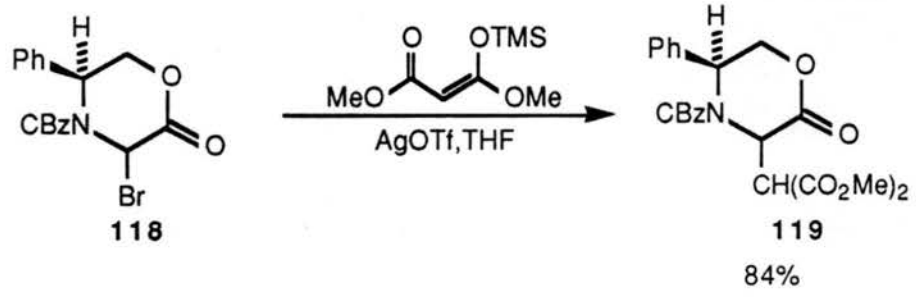
Equation 9

Having prepared electrophilic glycinate **110** a coupling reaction could now be attempted. Addition of silver trifluoromethansulfonate (the Lewis acid of choice in the piperazinedione studies) to a THF solution of **110** and the silyl ketene acetal of dimethylmalonate led to the formation of the homologated oxazinone **119**, as expected. ^1H NMR analysis of the adduct underscored what was to be a recurring problem, namely, that the spectra of N-acyl-tetrahydro-1,4-oxazin-2-ones are characterized by broad, ill-defined absorptions. Presumably, the source of the problem is hindered slow rotation of the urethane moiety on the NMR time scale about the C-N bond. Removal of the CBz group (H_2, 10% Pd/C) gave the free amine **120** (Scheme 38). This compound behaved "normally", giving sharp signals in the corresponding spectrum. ^1H NMR analysis indicated approximately a 2:1 mixture of diastereomers.

SCHEME 38



The success of the initial coupling reaction was encouraging despite the rather low stereoselectivity. However, as preparation of **110** from bromide **118** required the use of an expensive reagent (2-mercaptopyridine), and resulted in considerable loss of material, it was appropriate to attempt a coupling reaction using the crude bromo compound. Coupling does indeed take place with this molecule. In this case, **119** was isolated in 84% yield, again as a mixture of diastereomers (Equation 10).

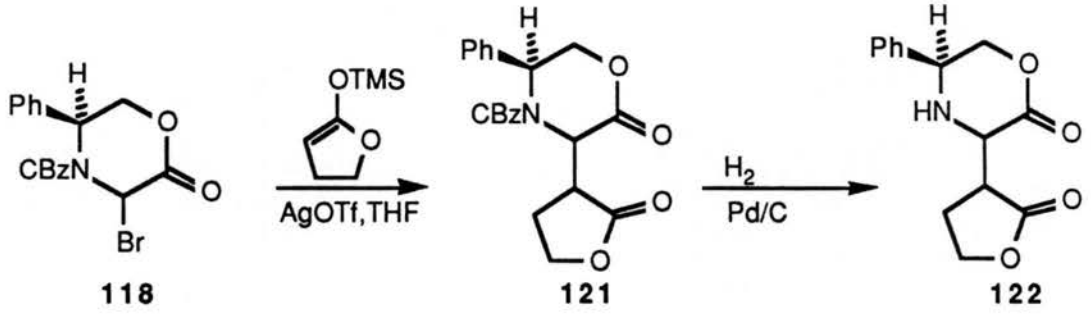


Equation 10

A second homologated oxazinone was prepared, this time using the silyl ketene acetal of γ-butyrolactone. Again the reaction proceeds readily to give **121** in 68% yield. ^{1}H NMR analysis of the free amine **122** indicated a mixture of at least two diastereomers

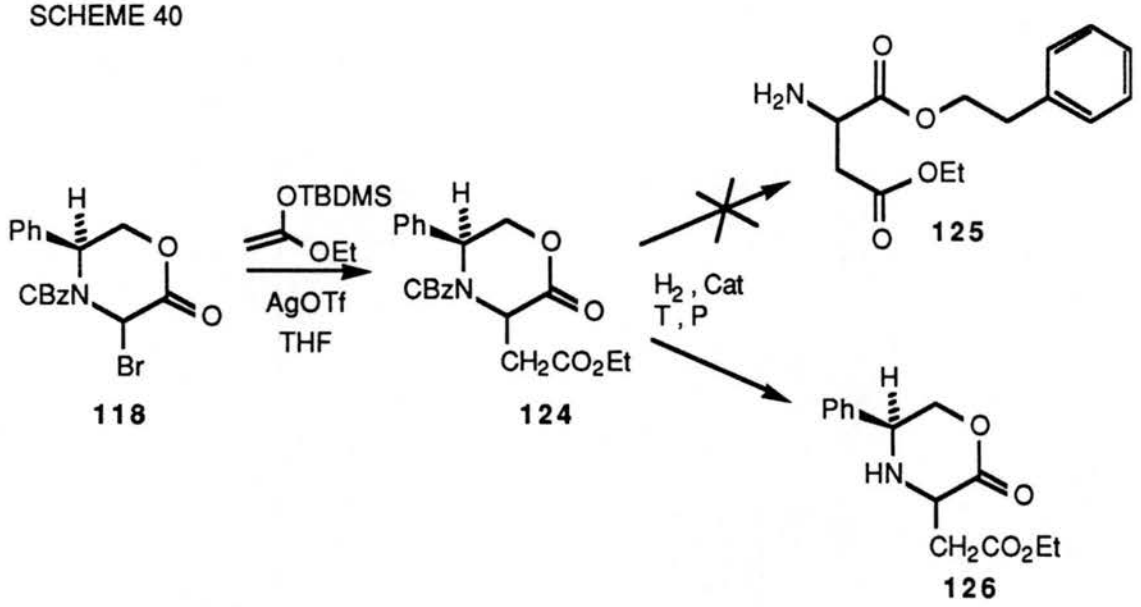
(Scheme 39). Having successfully demonstrated the ability to homologate the heterocycle with silyl ketene acetals, it was now necessary to examine the deprotection to the corresponding amino acid.

SCHEME 39



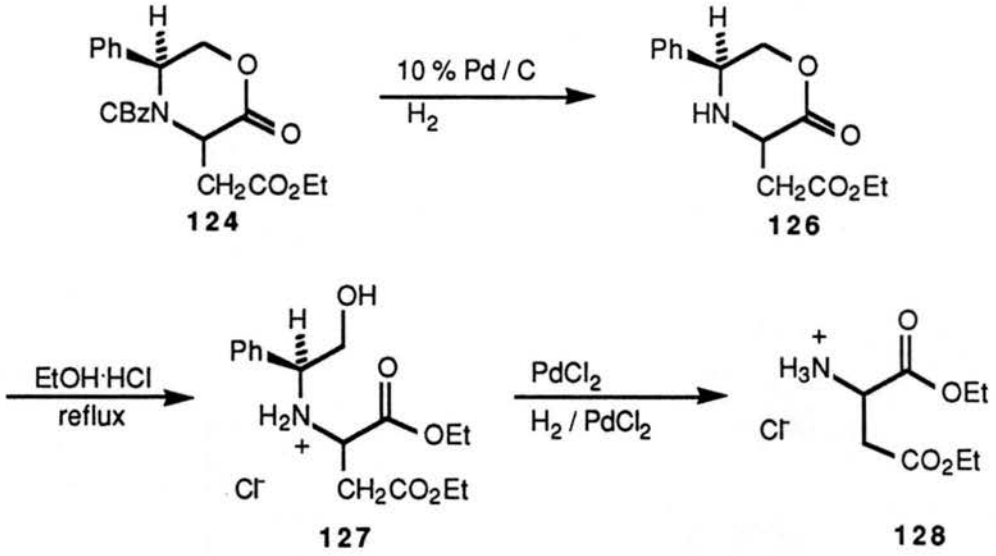
The two homologated oxazinones thus far prepared were not appropriate model compounds for deprotection studies. Malonate derivative **119** would be cleaved to an ester of β-carboxyaspartic acid, a recently identified but very unstable natural amino acid. The butyrolactone derivative would afford an unknown amino acid upon deprotection. Also, the second stereogenic center would exacerbate the problem of determining the stereoselectivity of coupling. The preparation of the natural amino acid aspartic acid was chosen in order to ease characterization. Condensation of **118** with the silyl ketene acetal of ethyl acetate **123** gave the desired amino acid precursor **124** in 65% yield as a 16:1 mixture of diastereomers. As previously mentioned, hydrogenation was expected to remove the CBz group and cleave the benzylic C-N bond to give the phenethylester of the amino acid **125**. Deprotection was attempted using a variety of conditions, but in all cases only the free amine **126** was obtained (Scheme 40).

SCHEME 40

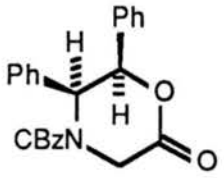


At this time Professor Dave Evans informed us of some results of interest. The Evans' group found that the derivatized compound (prepared in their group via enolate methodology) can be deprotected to the amino acid ester by first ring opening the heterocycle with ethanol-HCl and then hydrogenating the resultant hydrochloride salt. Oxazinone **126** was maintained at reflux in ethanol-HCl to give the amino ester hydrochloride **127**. Hydrogenation of **127** at 20 psi using $PdCl_2$ as catalyst resulted in deprotection to diethyl aspartate hydrochloride **128** (Scheme 41).

SCHEME 41



Having successfully prepared diethyl aspartate the viability of the overall synthetic scheme was demonstrated. However, the methodology was not without problems. The diastereoselectivity of coupling was low but it was believed that the selectivity could be improved by manipulation of conditions. The major obstacle was the unwieldly, three-step deprotection procedure. This was unacceptable! The erythro 5,6-diphenyl-tetrahydro-1,4-oxazinone **108** was chosen as the next amino acid template. It was reasoned that the



108a

the added phenyl ring would increase the stereoselectivity of coupling by adding steric bulk to the top face of the molecule. It was also anticipated that creation of a third benzyl carbon-heteroatom bond would solve the deprotection difficulties. The results of this approach are given in the next chapter.

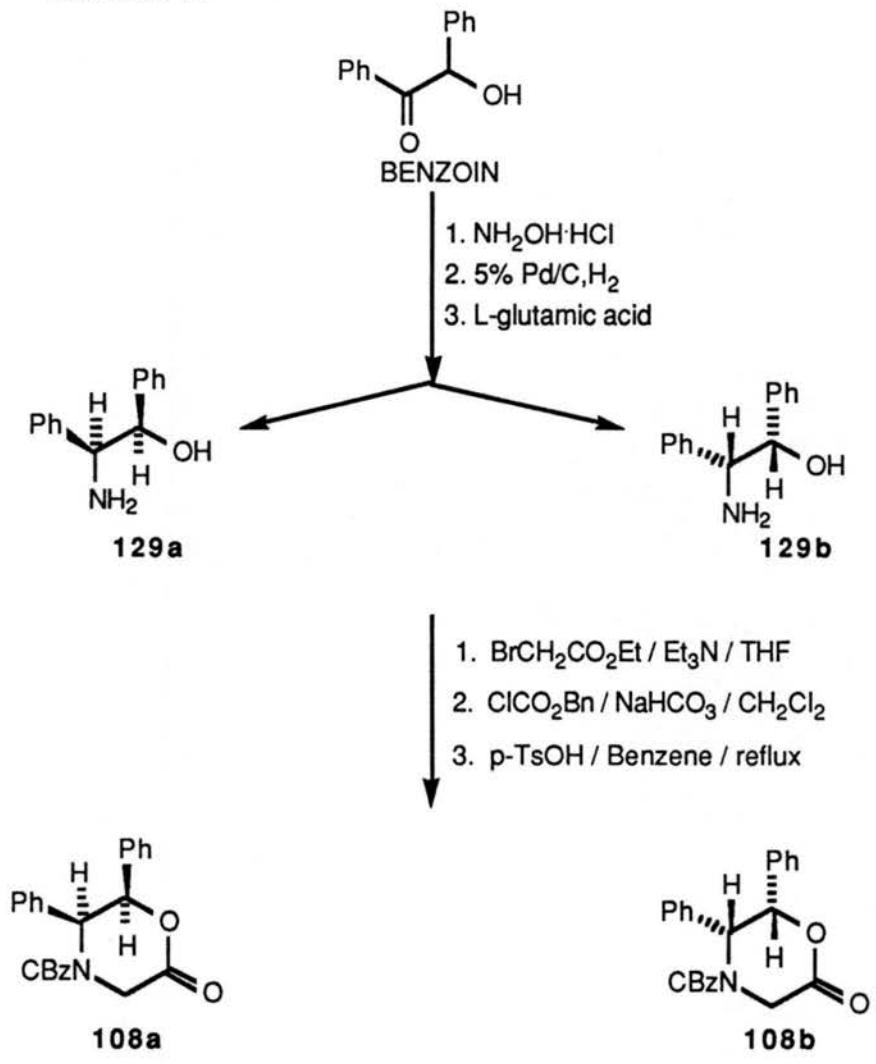
CHAPTER III

ERYTHRO-5,6-DIPHENYL-2,3,5,6-TETRAHYDRO-1,4-OXAZIN-2-ONES AS AMINO ACID TEMPLATES

A. Erythro-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-ones As Amino Acid Templates

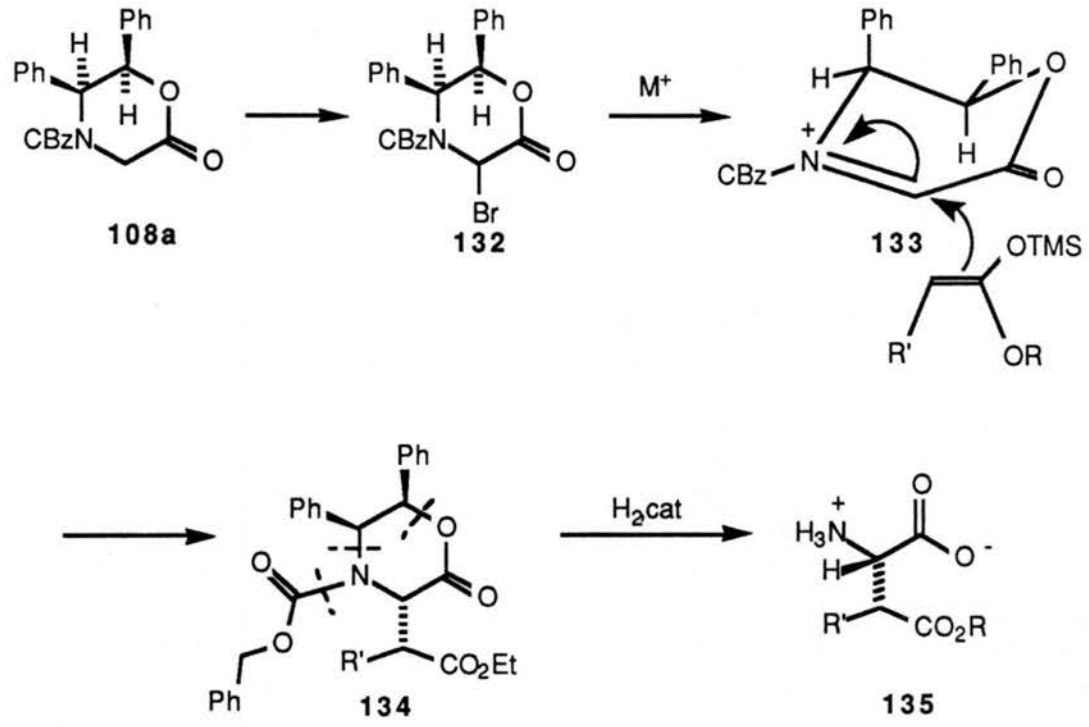
Having successfully achieved the synthesis of an α-amino acid ester using tetrahydrooxazinone **106** by activating the heterocycle towards substitution, coupling with a silyl ketene acetal, and subsequent deprotection of the homologated compound, the second generation amino acid template erythro-4-benzyloxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one **108** was now examined. Oxazinones **108a** and **108b** were prepared from the D- and L-erythro-α,β-diphenyl-β-hydroxyethylamines **129a** and **129b**, respectively (Scheme 42). The amino alcohols were obtained according to the method of Tishler et al.[41] involving the catalytic reduction of benzoin oxime followed by resolution with L-glutamic acid. Derivatization as the corresponding camphanic acids and HPLC analysis showed the amino alcohols were obtained ≥99% enantiomerically pure. As in the phenylglycinol series, condensation of **129a,b** with ethylbromoacetate afforded the corresponding amino esters **130a,b**. N-Acylation (benzylchloroformate, Schotten-Baumann conditions) followed by ring closure (pTsOH, benzene, reflux) gave the oxazinones in 70% yield from **129**.

SCHEME 42



The use of **108** as the amino acid template was anticipated to offer a two-fold advantage over template **107**: first, the additional steric shielding due to the presence of the second phenyl ring should increase the π-face selectivity of attack of the putative imminium ion **133** on the silyl ketene acetal. Second, the creation of a third benzylic carbon-heteroatom bond should permit a one-step reductive deprotection procedure. As with Kagan's synthesis,[18] catalytic hydrogenation of oxazinone **134** should cleave all three susceptible benzylic residues to afford the α-amino acid zwitterion **135** directly, as illustrated for the D-series heterocycle in Scheme 43.

SCHEME 43

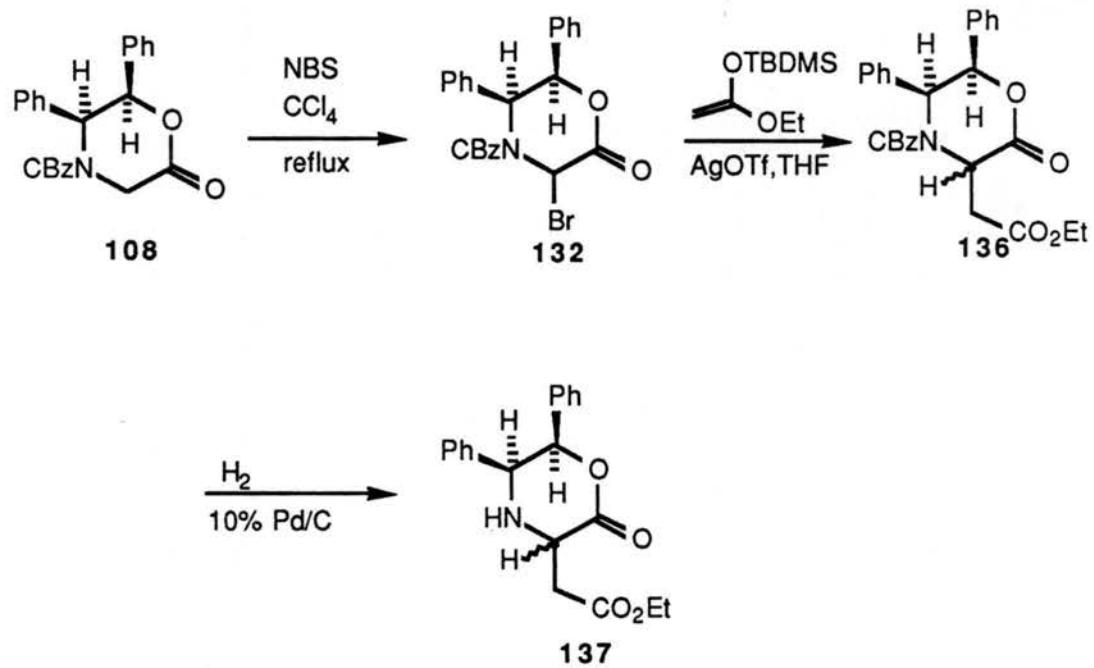


It is appropriate here to address two possible criticisms of the amino acid synthesis as outlined in Scheme 43: first, that the synthesis involves the loss of the chiral auxiliary and second, it requires a resolution step. While the reductive deprotection does take place with the concomitant destruction of the chiral auxiliary, the starting materials for this synthesis are so inexpensive (benzoin 2.5¢/g) that this is not deemed a drawback to utilization of this methodology. It is also true that the method described ultimately relies on the resolution of a racemic mixture in order to obtain enantiomerically pure compounds. However, the resolution step is straightforward, is carried out at the start of the synthesis, and utilizes cheap ($10/kg) and non-toxic L-glutamic acid as the resolving agent. Moreover, by virtue of the resolution the synthesis of both the D- and L-antipodes of α-amino acids is possible. Thus, since the method is targeted at a general synthesis of either

D- or L-amino acids, the resolution is in fact a powerful advantage rather than a drawback to the approach.

Oxazinone **108** was expected to brominate as readily as **107**. Indeed, **108** smoothly undergoes bromination (NBS, CCl_4, reflux) to give, after workup, bromide **132** as a pure white solid in essentially quantitative yield (Scheme 44). Again, the bromide proved unstable to silica gel chromatography and was allowed to react crude. Subjecting **132** to the coupling conditions developed for bromide **118** resulted in immediate formation of the homologated product **136**. The reaction was remarkably clean showing only one spot by TLC. As in the phenylglycinol series, ^1H NMR analysis was difficult due to broadened absorptions (Figure 1). The ^1H NMR spectrum of free amine **137** indicated that the desired product had been obtained but as a disappointing 2:1 mixture of diastereomers (Figure 2). It became clear that the coupling conditions would have to be modified in order to achieve higher stereoselectivity.

SCHEME 44



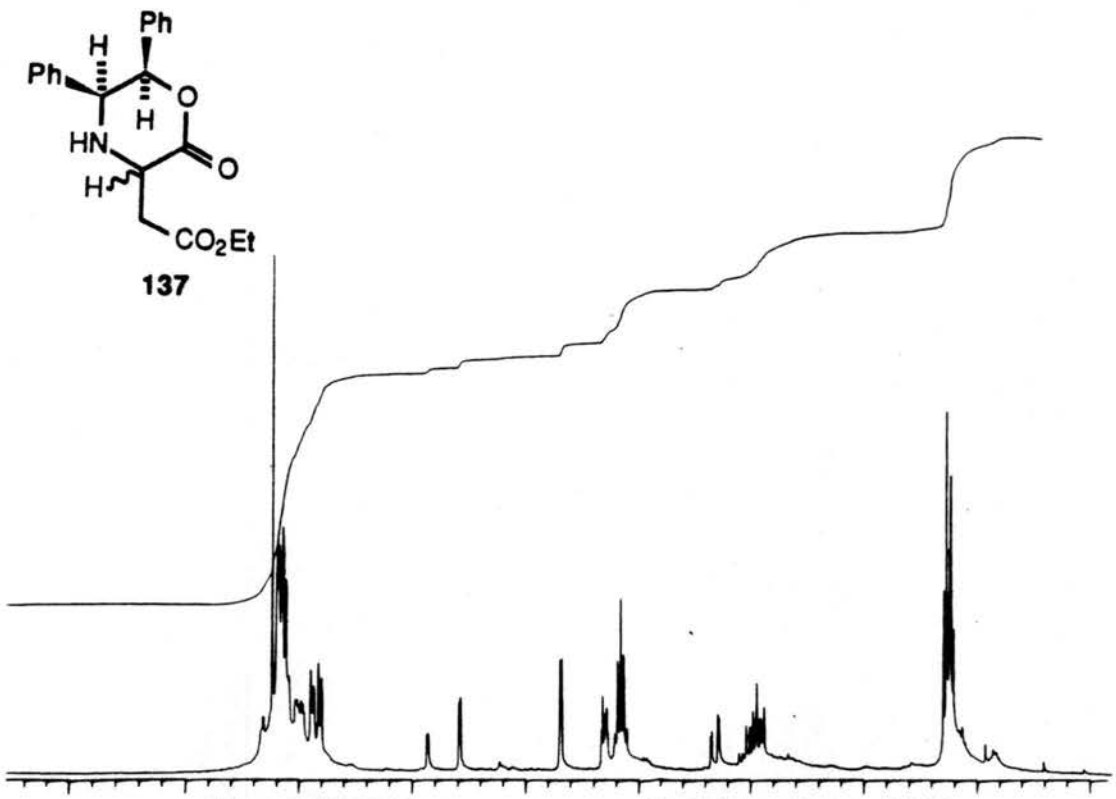


Figure 2 ^{1}H NMR (270 MHz) of **137** (AgOTf coupling) in $CDCl_3$

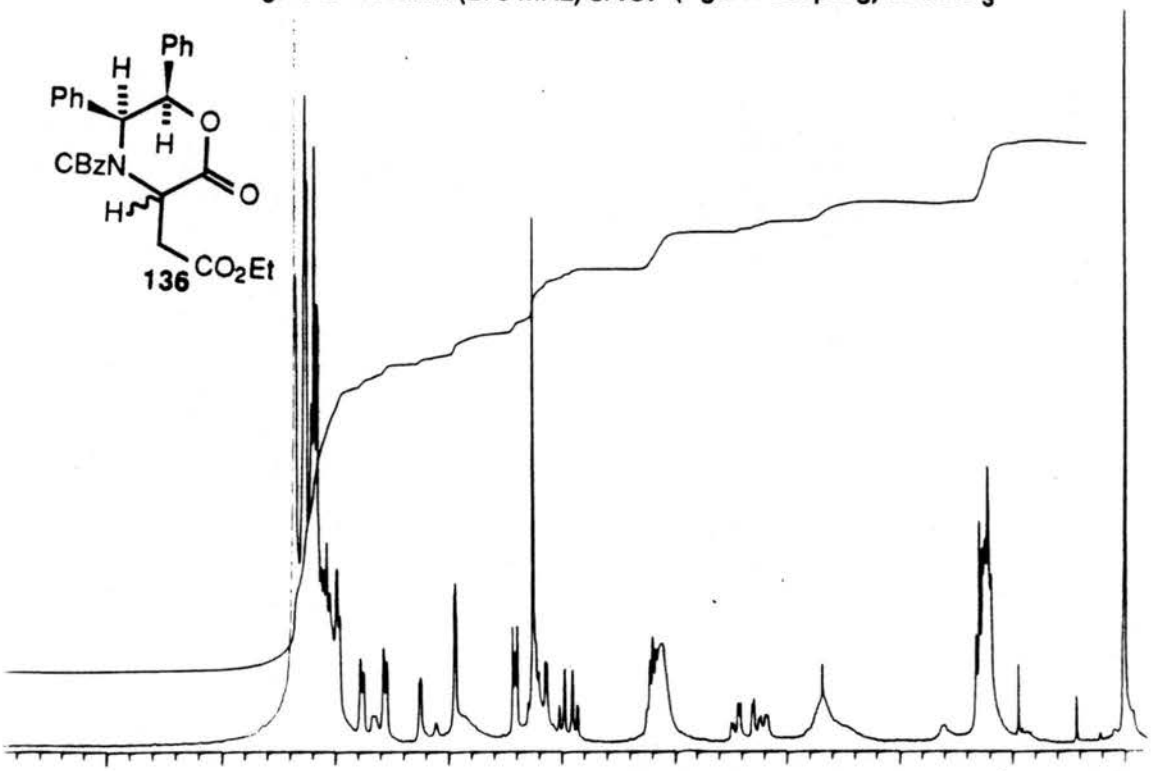
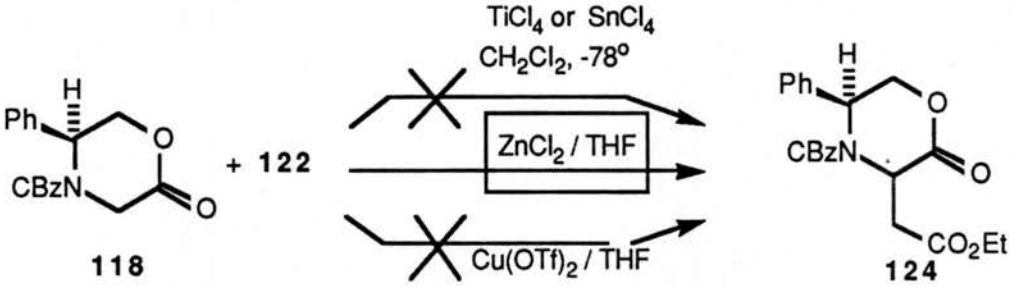


Figure 1 ^{1}H NMR (270 MHz) of **136** (AgOTf coupling) in $CDCl_3$ at 25°c.

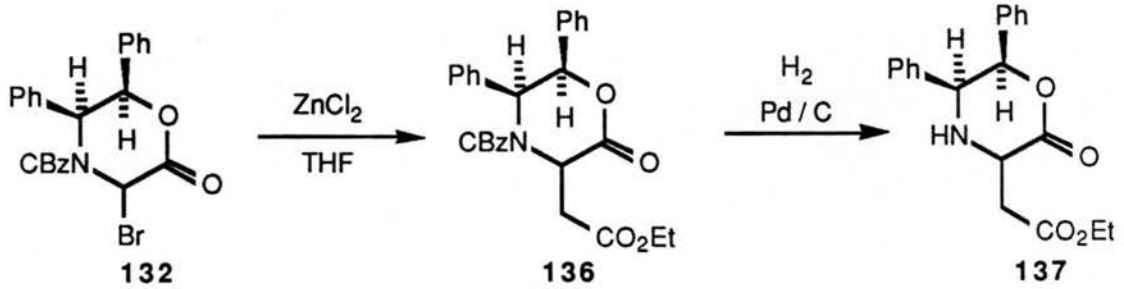
A cursory investigation into the effect of using alternate Lewis acids in the coupling reaction was carried out on the phenylglycinol derived bromoglycinate **118**. The presence of the hard Lewis acids $TiCl_4$ or $SnCl_4$ in the reaction mixture led only to substrate decomposition. Copper trifluoromethanesulfonate did not induce decomposition but also did not mediate carbon-carbon bond formation. However, coupling was smoothly effected by $ZnCl_2$ to give the homologated oxazinone **124** (Scheme 45).

SCEME 45

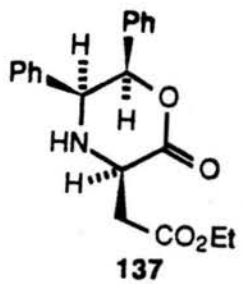


Homologation of bromoglycinate **132** was then carried out using $ZnCl_2$ as the Lewis acid (Scheme 46). The coupling took place and afforded **136** in 64% yield. ^1H NMR analysis of **136** gave a simple yet still undefined spectrum (Figure 3). The ^1H NMR spectrum of free amine **137** indicated that only one diastereomer had been formed (Figure 4). This result was encouraging and the deprotection was now examined.

SCHEME 46

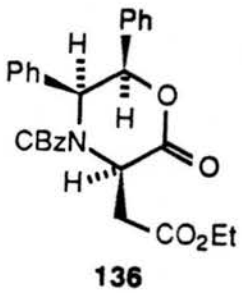


As in Kagan's synthesis of aspartic acid,[18] catalytic hydrogenation was expected to cleave the heterocycle and give the amino acid zwitterion directly. Oxazinone **136** was



137

Figure 4 ^{1}H NMR (270 MHz) of **137** ($ZnCl_2$ coupling) in $CDCl_3$ at 25°c.

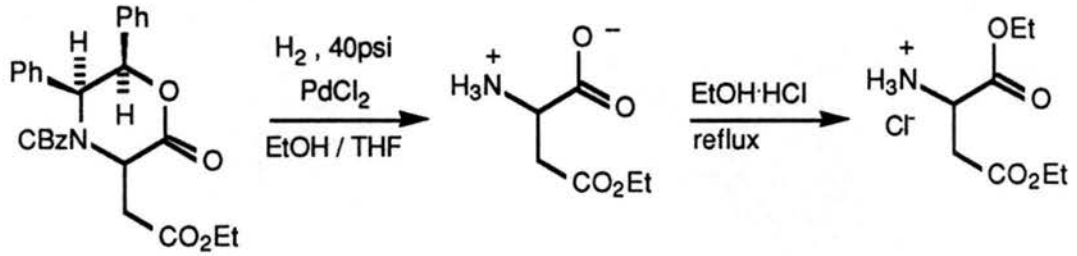


136

Figure 3 ^{1}H NMR (270 MHz) of **136** ($ZnCl_2$ coupling) in $CDCl_3$ at 25°c.

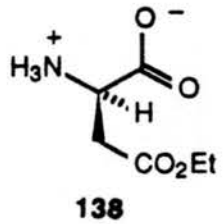
hydrogenated as 20 psi for 24 hours in the presence of $PdCl_2$. The mixture was filtered, concentrated and the residue triturated with Et_2O to afford β-ethyl aspartate **138** as a white solid (Scheme 47). The ^1H NMR spectrum of **138** showed no impurities (Figure 5). Esterification (EtOH·HCl, reflux) gave diethyl aspartate hydrochloride **139** (Figure 6). The deprotection not only worked as envisioned, but it also gave the amino acid zwitterion in high yield, and required minimal purification.

SCHEME 47



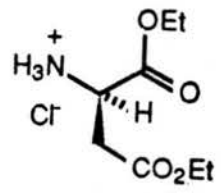
136 **138** **139**

Silyl ketene acetals were anticipated to readily couple to the electrophilic glycinate and it was desirable to determine what other reagents would undergo carbon-carbon bond formation with **132**. A brief survey of reagent types that may undergo coupling was initiated. Not surprisingly, the silyl enol ether of acetophenone **140** coupled with bromide **132** ($ZnCl_2$, THF) to give the homologated heterocycle **141** (Scheme 48). Hydrogenolysis of **141** took place with concomitant reduction of the ketone carbonyl to furnish homophenylalanine **142**.



138

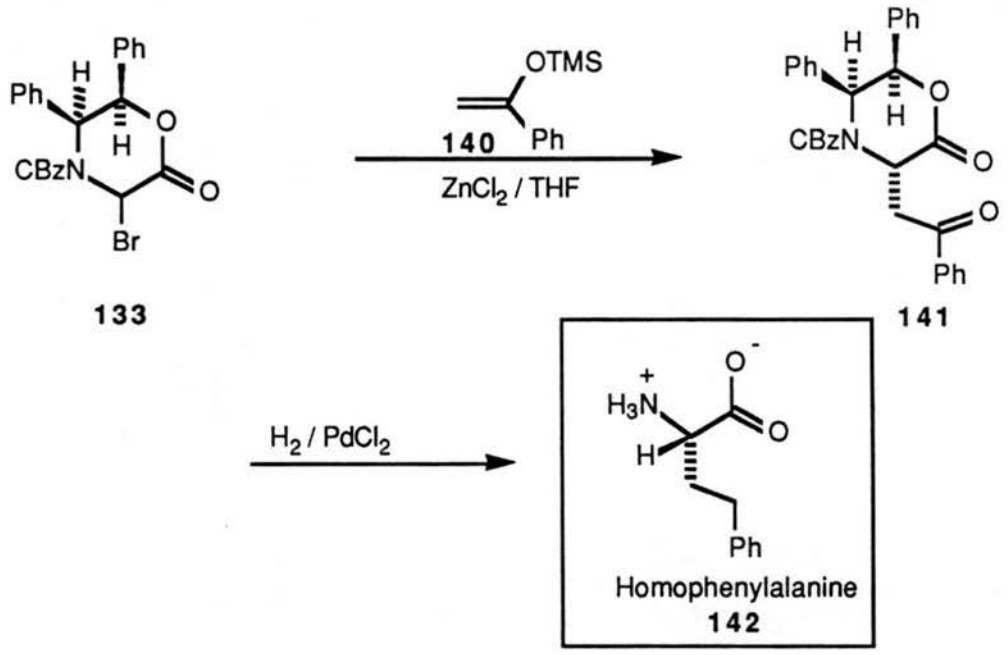
Figure 5 ^{1}H NMR (270 MHz) of **138** in D_2O.



139

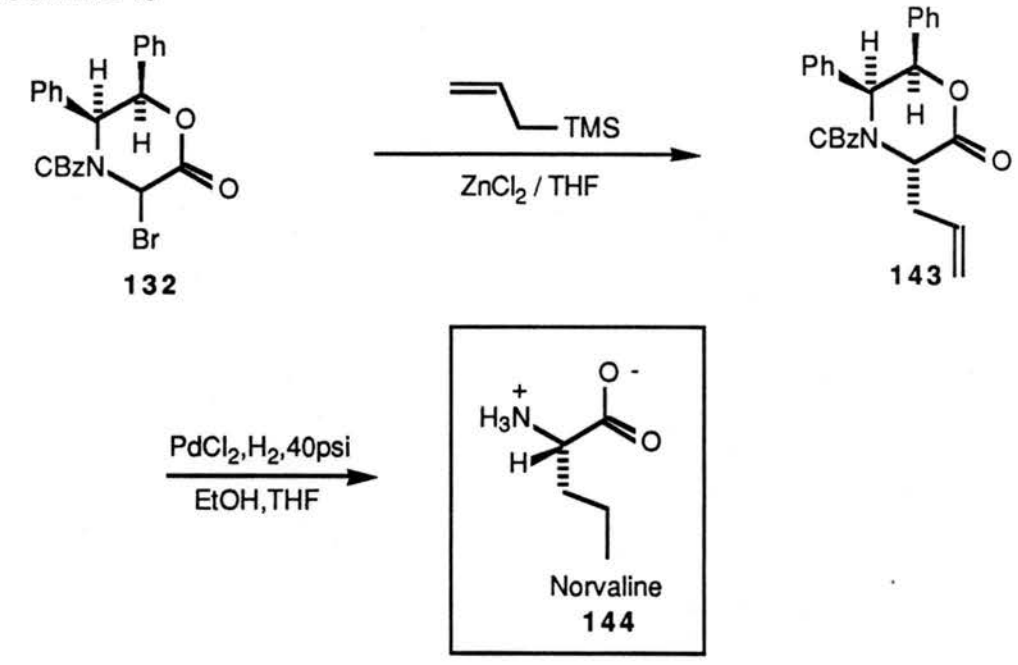
Figure 6 ^{1}H NMR (270 MHz) of **139** in D_2O

SCHEME 48

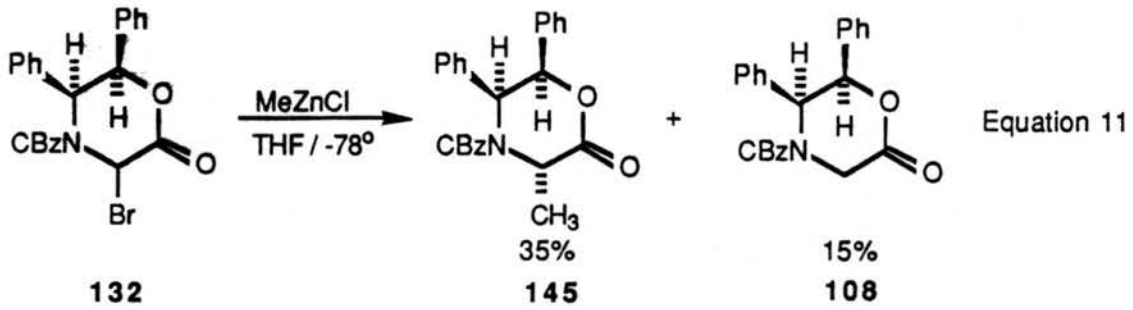


Allyl silanes, although not as reactive as silyl ketene acetals or silyl enol ethers, are also readily susceptible to electrophilic attack. Coupling of allyltrimethylsilane with **132** ($ZnCl_2$, THF) was effected giving the corresponding allyl oxazinone **143** (Scheme 49). This reaction was markedly slower than the preceeding two, taking several days, but afforded the desired compound in 68% yield. Hydrogenation of **143** gave the amino acid norvaline **144** as a pure white solid.

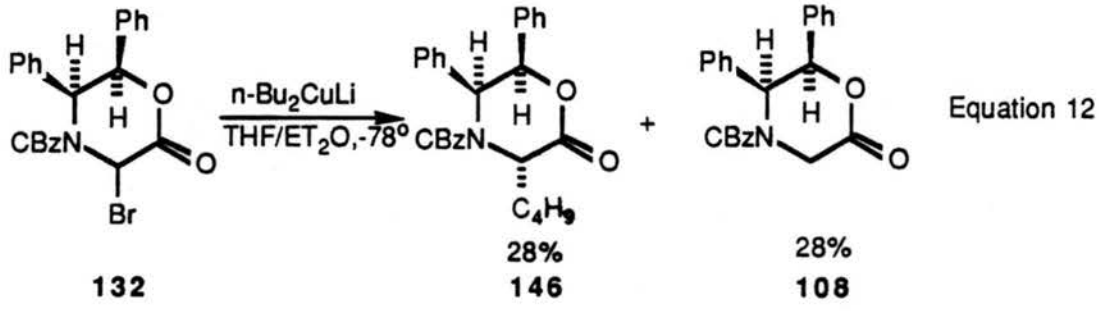
SCHEME 49



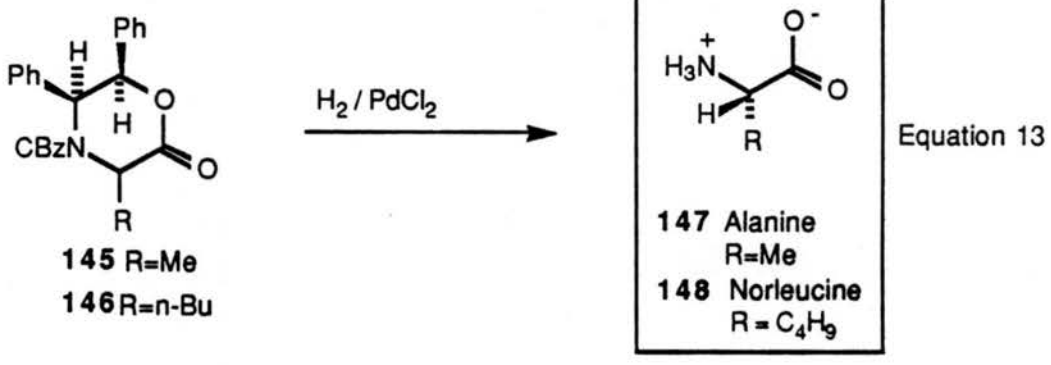
The use of $ZnCl_2$ as the Lewis acid in these reactions suggested examining the homologation of the bromoglycinate using alkyl zinc reagents. The addition of MeZnCl to a THF solution of **132** at -78° afforded the corresponding methyl oxazinone **145**. Unfortunately, the yield of the homologated heterocycle was low (~30%) with reduction of the bromide and decomposition being major side reactions (Equation 11). Dialkyl lithium cuprates and higher order mixed cuprates were also examined as coupling reagents. As with methyl zinc chloride the coupling of di-n-butyllithium cuprate with **132** to give oxazinone **146** was accompanied by extensive reduction and decomposition (Equation 12). The homologated oxazinones **145** and **146** were deprotected to the corresponding amino acids alanine **147** and norleucine **148**, respectively (Equation 13). While alkyl zinc and alkyl cuprates afforded some coupled product, the use of Grignard and alkyllithium reagents in the coupling reaction led only to reduction and decomposition.



132 **145** **108**



132 **146** **108**



145 R=Me
146 R=n-Bu

147 Alanine R=Me
148 Norleucine R = C_4H_9

The preceeding reactions, carried out using racemic oxazinone **108**, demonstrated the feasibility of the synthetic method described. The selectivity of the coupling reactions now needed to be examined. Specifically, the absolute stereochemistry of the newly formed stereogenic center and the degree of diastereoselectivity achieved needed to be determined. ^{1}H NMR analysis of the homologated oxazinones was not suitable for reasons previously mentioned. The free amine compounds (obtained by removal of the CBz group) give characteristically well resolved spectra, but are difficult to obtain because of the

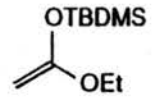
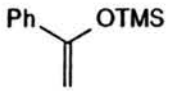
problem of over reduction accompanied by ring cleavage. The best way to determine selectivity was to prepare and characterize the optically active amino acids.

The five coupling reactions described above were repeated using the optically active oxazinone **108a** derived from D-erythro-diphenylethanolamine **129a**. Using this substrate the L-antipode of the amino acids was expected to be formed, as shown in Scheme 43. Hydrogenation of the homologated heterocycles furnished the optically active amino acids listed in Table II. The β-ethylaspartate derived from oxazinone **129a** was esterified (EtOH·HCl/reflux) and the optical rotation of the synthetic diethyl aspartate hydrochloride indicated that the amino acid possessed the unnatural D-(2R) configuration ($[\alpha]_D$ = -7.4 (c = 1, H_2O); authentic L-diethylaspartate hydrochloride $[\alpha]_D$ = +7.6 (c = 1, H_2O). Either the absolute configuration of the starting amino alcohol was incorrectly assigned, or the homologated oxazinone **136a** possessed the all syn configuration.

A single crystal x-ray structure of racemic allyl oxazinone **143** clearly showed the expected anti relationship between the two phenyl rings on the heterocycle and the allyl group (Figure 7). The optically active norvaline proved to have the L-(2S) configuration. Therefore it was concluded that the ethyl acetate silyl ketene acetal coupled from the most hindered face of the molecule to give the syn diastereomer of **136** (Equation 14). The mechanistic implications of this anomolous behavior are discussed later.

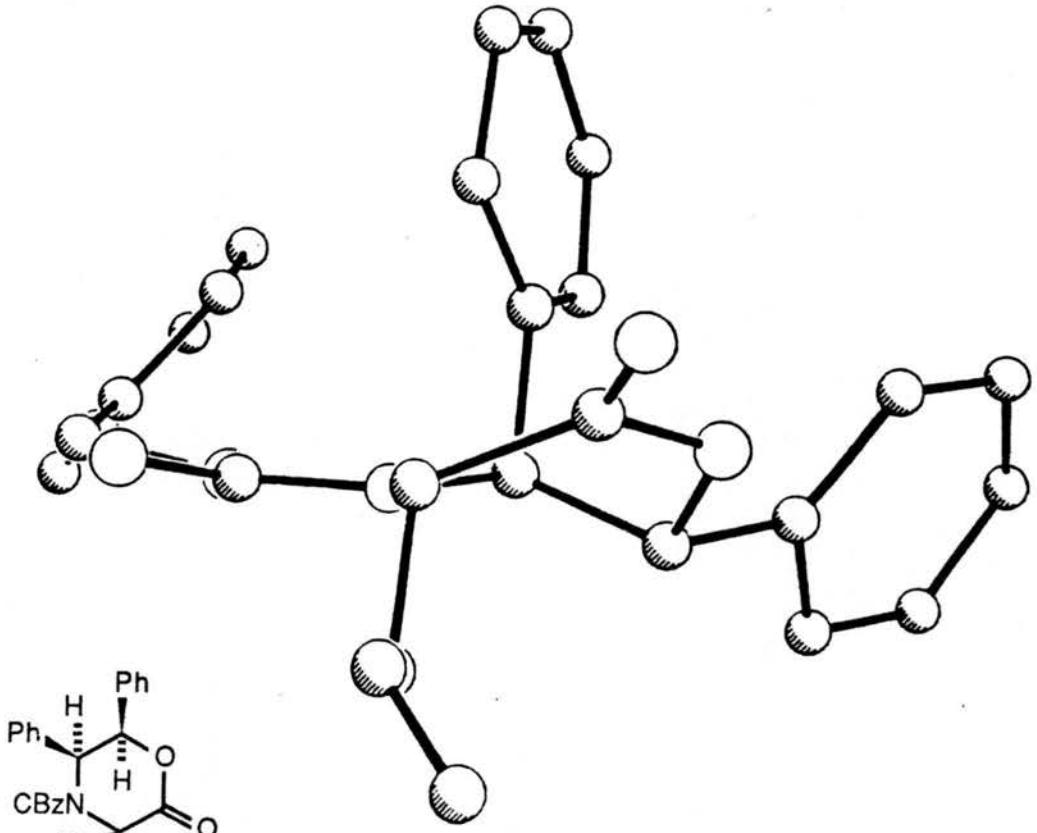
Like norvaline, the amino acids homophenylalanine, alanine, and norleucine also possessed the expected L-configuration. The enantiomeric excess of each amino acid was determined by acylation of the corresponding ethyl ester with either (+)- or (-)-α-methoxy-α-trifluoromethyl phenyl acetyl chloride[25] and examination of the crude mixture by ^{19}F NMR and comparison with the authentic diastereomeric mixture obtained from the racemic amino acids. In each case excellent stereoselectivity was observed.

TABLE II

REAGENT	REACTION CONDITIONS	YIELD	AMINO ACID	% e.e.
	1.2 $ZnCl_2$ THF 25° 1hr	71%	D- β -ethylaspartate	96.6
	1.2 $ZnCl_2$ THF 25°	54% [a]	homophenylalanine	96.9 [b]
	2 $ZnCl_2$ THF 25° 3 days	68%	L-norvaline	98.3
MeZnCl	THF -78° 30 min	46%	L-alanine	96.8
$Bu_2CuCNLi_2$	THF/Et_2O -78° 30 min	48%	L-norleucine	99.5

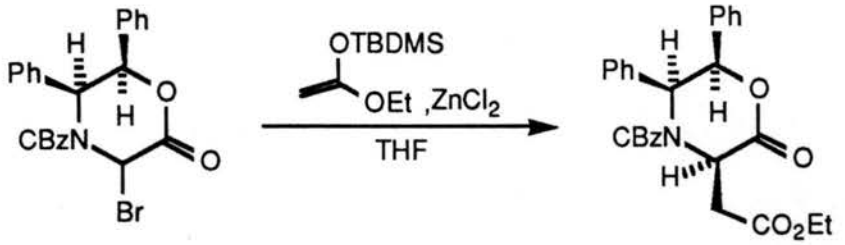
[a] Oxazinone obtained as a 7:1 mixture of diastereomers.

[b] e.e. obtained after crystallization of oxazinone.



143

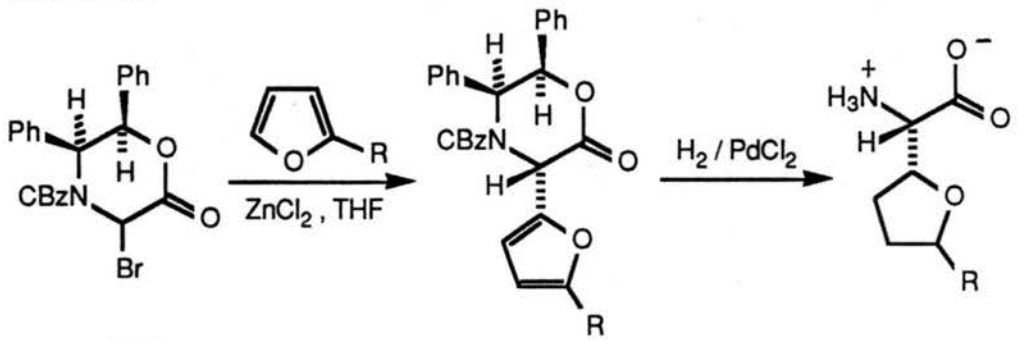
Figure 7 Stereostructure of **143**. Atoms are spheres of fixed arbitrary radius. Hydrogen atoms are not shown for clarity.



133a **137a** Equation 14

Coupling to the electrophilic glycinate seems to work best with neutral or nonbasic organometallic reagents. Electron rich heteroaromatics such as furan and substituted furans couple readily. The resulting oxazinones can be hydrogenated to furnish the corresponding tetrahydrofuryl glycines (Scheme 50). Tetrahydrofuryl glycine **151** was obtained as an approximately 5:1 mixture of diastereomers. While no rigorous proof of stereochemistry at the 2'-carbon was made, one can reason that the amino acid should adopt a conformation that favors hydrogen bonding between the amine hydrogens and the ring oxygen (Figure 8). Coupling constants between H_a and H_b indicate that the second stereogenic center has the R configuration. The (5'-methyltetrahydrofuryl) glycine **152**, having 3 stereogenic centers, is obtained as a complex mixture of diastereomers.

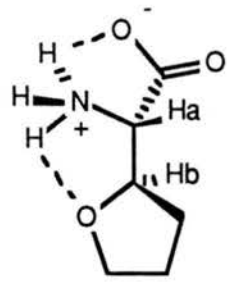
SCHEME 50



132

149 R=H
150 R=Me

151 R=H
152 R=Me

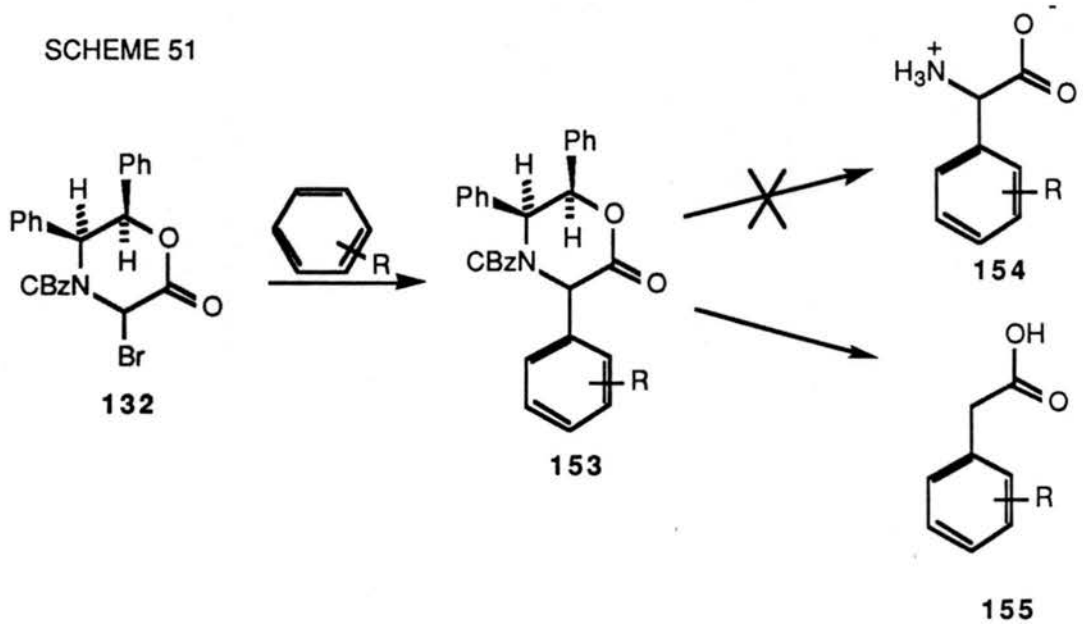


2S,2'R
$J_{a,b}$=3.9 Hz

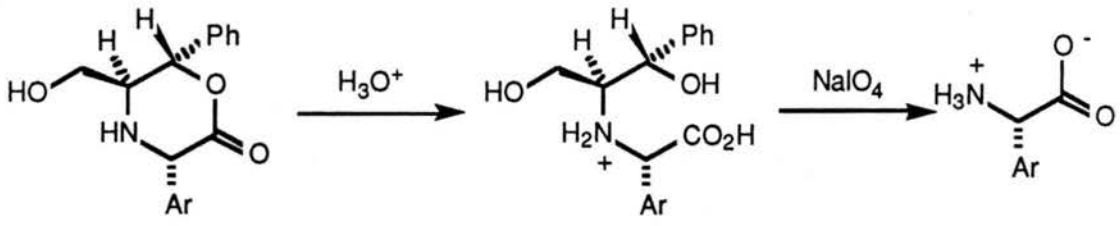
Figure 8

While heteroaromatic derivatives of oxazinone **108** have been prepared and successfully deprotected to the saturated amino acids, the corresponding phenyl derivatives of **108** have not. Although it is desirable to be able to prepare phenylglycine analogues, creation of a fourth benzylic carbon-heteroatom bond by coupling a phenyl ring to bromoglycinate **132** precludes the use of a reductive deprotection as the reaction is not expected to exhibit any bond cleavage specificity (Scheme 51). A promising procedure that may allow preparation of phenyl glycine derivatives is the oxidative deprotection developed by Weinges,[22] of the 1,4-oxazine-2-ones **40** synthesized by a Strecker synthesis (Scheme 52). Work is proceeding in this area.

SCHEME 51



SCHEME 52



40 **134**

The heterocycle (5S,6R)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazine-2-one **108a** has proven to be a workable template for amino acid synthesis. Bromoglycinate **132**, readily obtained from **108a**, couples with a variety of reagents to give the corresponding homologated heterocycles in moderate to good yields. The deprotection is remarkably clean and efficient, requiring little workup, and directly affording the amino acid zwitterion in consistently high enantiomeric excess. Having demonstrated the viability of **108** as an amino acid precursor it was desirable to extend the scope of this methodology.

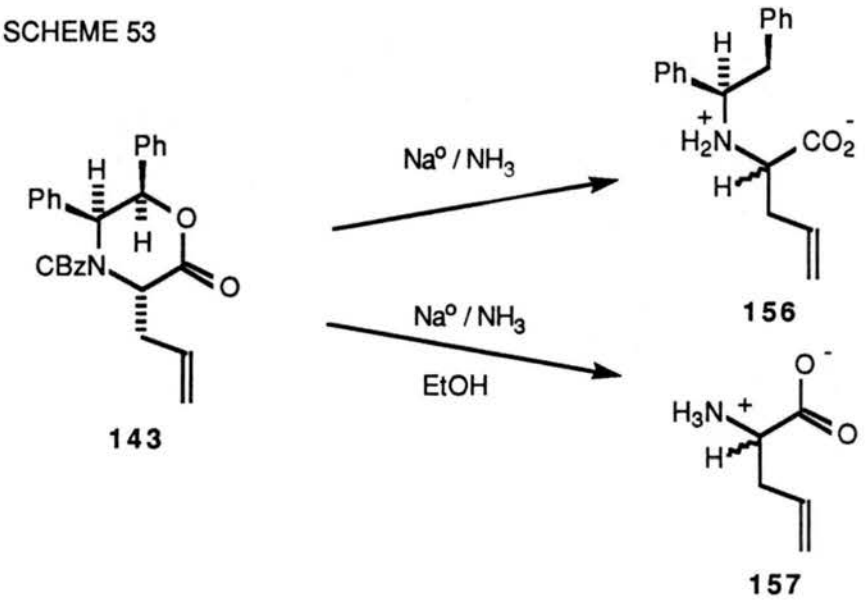
B. Preparation of Unsaturated Amino Acids

Many of the natural and synthetic amino acids that possess biological activity contain some unsaturation in the side chain. For example, vinyl glycine derivatives have been shown to be an important class of enzyme inhibitors.[42] While the hydrogenolysis deprotection procedure described is exceptionally facile, it precludes the direct synthesis of unsaturated amino acids. It was therefore desirable to develop an alternate deprotection procedure that is tolerant of olefinic bonds. For this dissolving metal reductions were chosen to be examined.

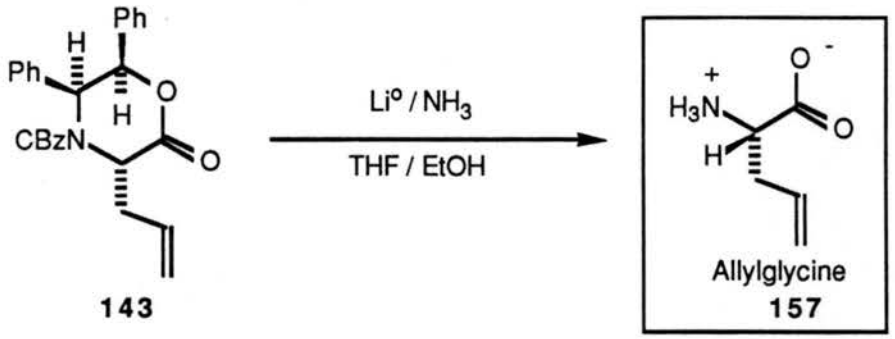
Sodium liquid ammonia reductions (Birch-type reductions) have been used for 50 years in peptide chemistry for the removal of benzyl- and tosyl-type protecting groups.[43] This electron transfer method was expected to cleave the benzylic carbon-nitrogen and carbon-oxygen bonds without reducing an isolated double bond. The major concern was whether racemization would take place under the basic conditions employed. The initial

studies were carried out on allyl oxazinone **143**. Addition of sodium metal to a suspension of **143** in liquid ammonia led only to formation of the N-alkyl amino acid **156** (Scheme 53). When the same reaction was carried out in the presence of ethanol, acting as a proton source, the desired amino acid allyl glycine **157** was obtained. Unfortunately, deprotection under these conditions was characterized by low yields attributed to poor substrate solubility in NH_3, and proceeded with attendant racemization.

SCHEME 53

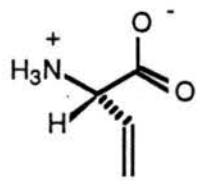


Both problems could be solved by reversing the order of reagent addition using lithium rather than sodium and by using THF as a cosolvent. Thus, addition of a THF solution of oxazinone **143** and EtOH to a solution of excess lithium metal dissolved in liquid ammonia smoothly led to the formation of allylglycine **157** (Equation 15). The reaction was quenched with excess ammonium chloride when the characteristic blue color of lithium/liquid ammonia reduction had dissipated. Isolation via ion exchange chromatography afforded the amino acid in 90% yield.



Equation 15

Analysis of the Mosher amide of the allyl glycine ethyl ester by ^{19}F NMR indicated no racemization had occurred. Preservation of the stereochemical integrity of the α-carbon was attributed to the fact that the benzylic carbon-oxygen bonds will cleave first, thus situating the stereogenic center α to a carboxylate anion and thereby increasing the pKa of the α-proton tremendously. The use of this methodology in the preparation of vinyl glycine derivatives (**158**) is currently being explored.



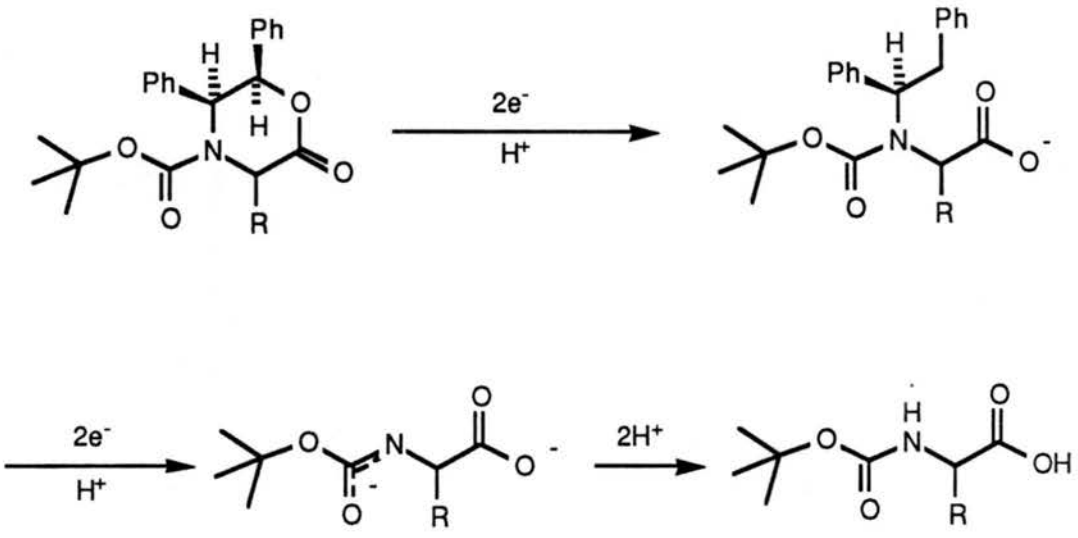
158

C. Preparation of t-BOC-Protected Amino Acids

Peptide synthesis requires the use of N-protected amino acids during peptide bond formation. Since the benzyloxycarbonyl (CBz) protecting group is cleaved during the reductive deprotection procedures, a modification of the synthesis was desired that would permit the direct synthesis of N-protected α-amino acids. The t-butoxycarbonyl (t-BOC) moiety is one of the preferred amino acid nitrogen protecting groups, and is easily cleaved upon treatment with acid. The t-BOC group is stable to base and, in particular, stable to dissolving metal reductions. In fact, cleavage of the benzylic carbon-nitrogen bond of the

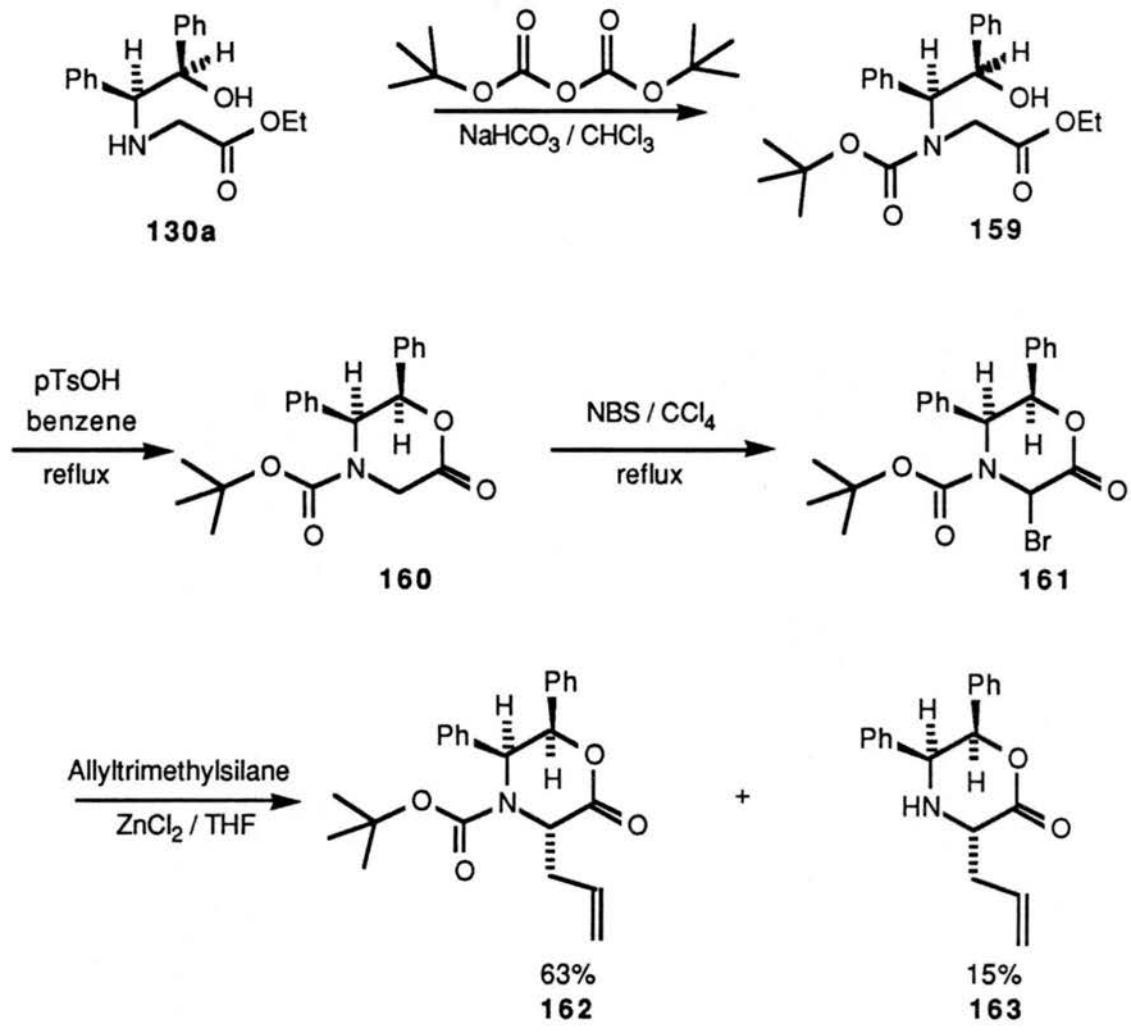
oxazinone by a Birch reduction should be facilitated by the t-BOC group through resonance stabilization of the incipient negative charge on nitrogen (Scheme 54).

SCHEME 54

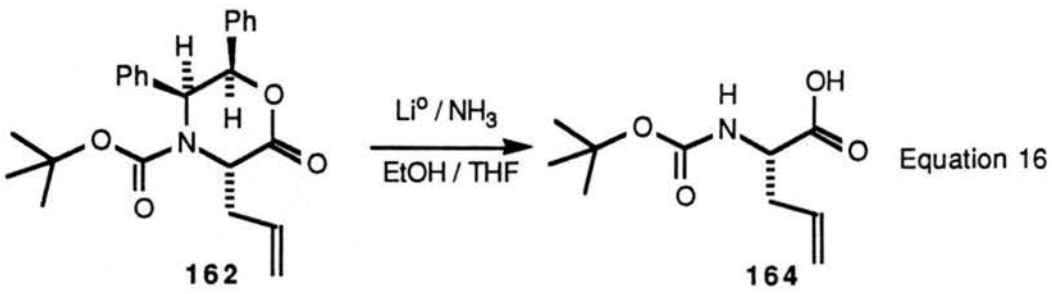


(5S,6R)-N-t-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one **160** was prepared in a manner analogous to **108**. Amino ester **130a** was acylated with di-t-butyl-dicarbonate under Schotten-Baumann conditions to give **159**. Acid catalyzed ring closure (pTsOH, benzene, reflux) gave oxazinone **160** in 46% yield from **130** as a pure white solid (Scheme 55). Bromination (NBS, CCl_4, reflux) generated the electrophilic glycinate **161**, obtained after workup as a white solid. Bromoglycinate **161** coupled with allyl trimethylsilane to give the corresponding allyl oxazinone **162**. A major side product obtained was the allyloxazinone **163** minus the t-BOC protecting group. Formation of **163** may be ascribed to the instability of the t-BOC group to Lewis acids generated during the course of the reaction (i.e., TMS-Cl, Zn^{++}).

SCHEME 55



Subjecting **159** to a dissolving metal reduction (Li/NH_3, EtOH, THF) resulted in formation of t-BOC allyl glycine **161** in 60-70% yield (Equation 16). The amino acid was esterified (EtOH·HCl) with concomitant removal of the protecting group. The Mosher amide of the amino ester was prepared and ^{19}F NMR analysis indicated the amino acid was prepared in ≥96% e.e. The lower yields of the isolated protected amino acids may be due to loss of the protecting group during acidification and extraction.



162 164 Equation 16

It is worth noting that oxazinone **160** with the base-stable nitrogen protecting group might make a better substrate for organometallic coupling reactions than the CBz protected heterocycle. This supposition has been substantiated by at least one example carried out in Williams' group.[44]

D. Synthetic Approaches to Biologically Important Amino Acids

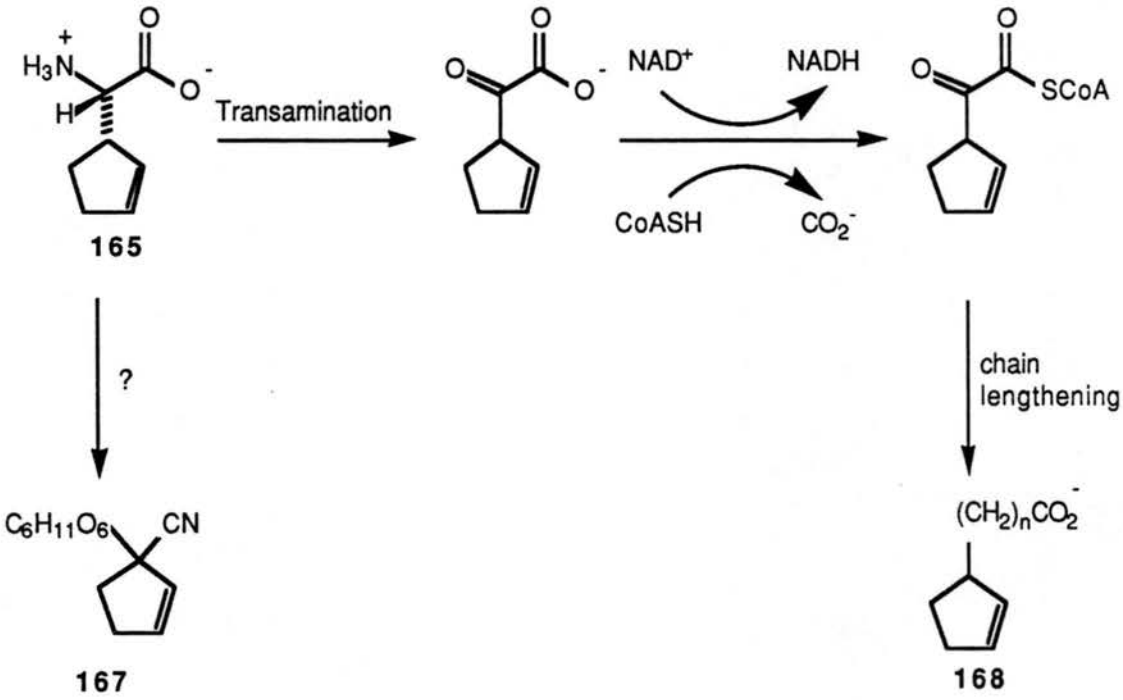
Having developed a general amino acid synthesis that affords the desired compounds in reasonably good yields and high enantiomeric excess it was desirable to utilize this methodology to prepare a number of biologically interesting amino acids. The following paragraphs briefly discuss the target amino acids and the synthetic approach to each.

Cyclopentenylglycine

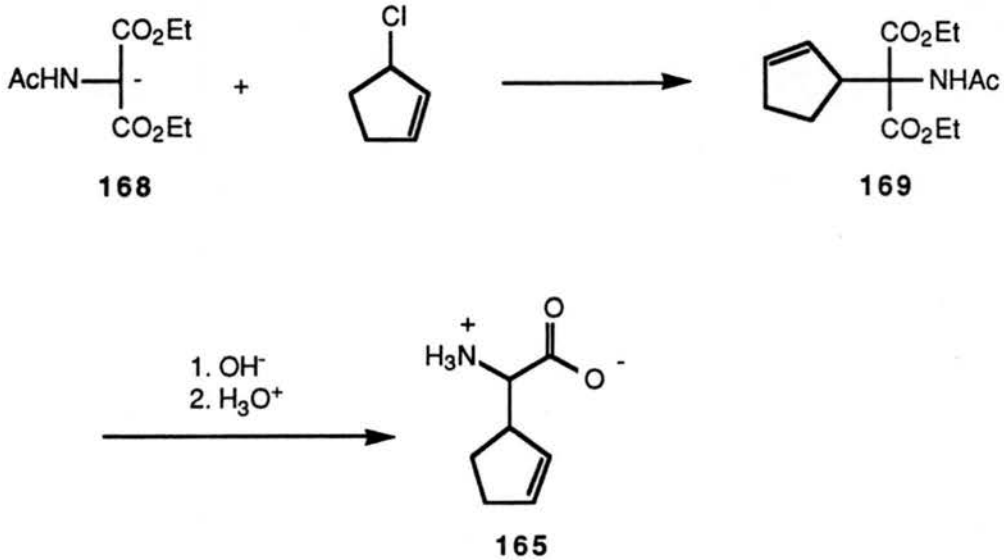
Cyclopentenylglycine **165** is a naturally occurring non-proteinogenic amino acid isolated from the seeds of *Hydnocarpus anthelminthica* and the leaves of *Caloncoba echinata*.[45] Racemic cyclopentenylglycine has been shown[46] to be a potent growth inhibitor of *E. coli* as well as a biogenic precursor of unusual cyclopentenyl fatty acids **166**[47] (Scheme 56). Cyclopentenylglycine has also been hypothesized to be a precursor of the cyanogenic glycoside deidaclin **167**.[48] The unsaturated amino acid has been prepared in racemic from via a Sörenson synthesis.[46] Condensation of 3-chlorocyclopentene with the acetamidomalonic ester anion **168** gave the malonate derivative **169**. Deprotection and

decarboxylation gave racemic **165** (Scheme 57). To date there have been no reported enantioselective syntheses.

SCHEME 56

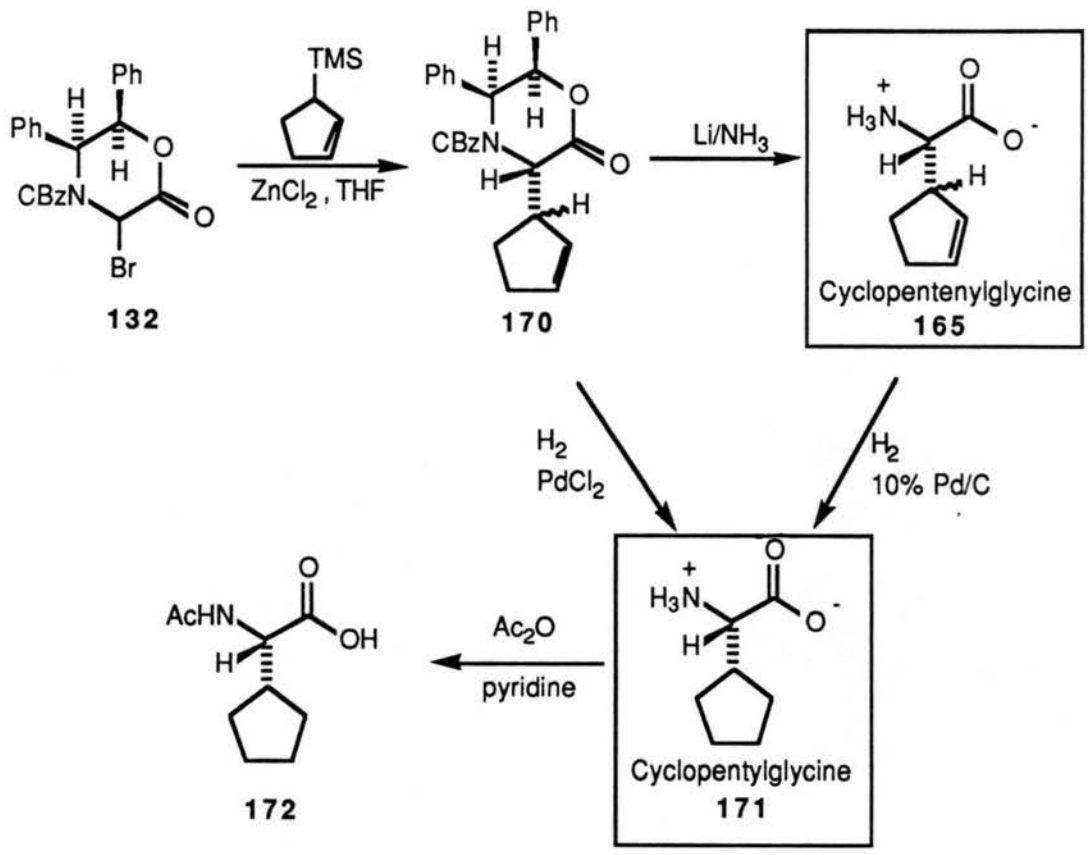


SCHEME 57



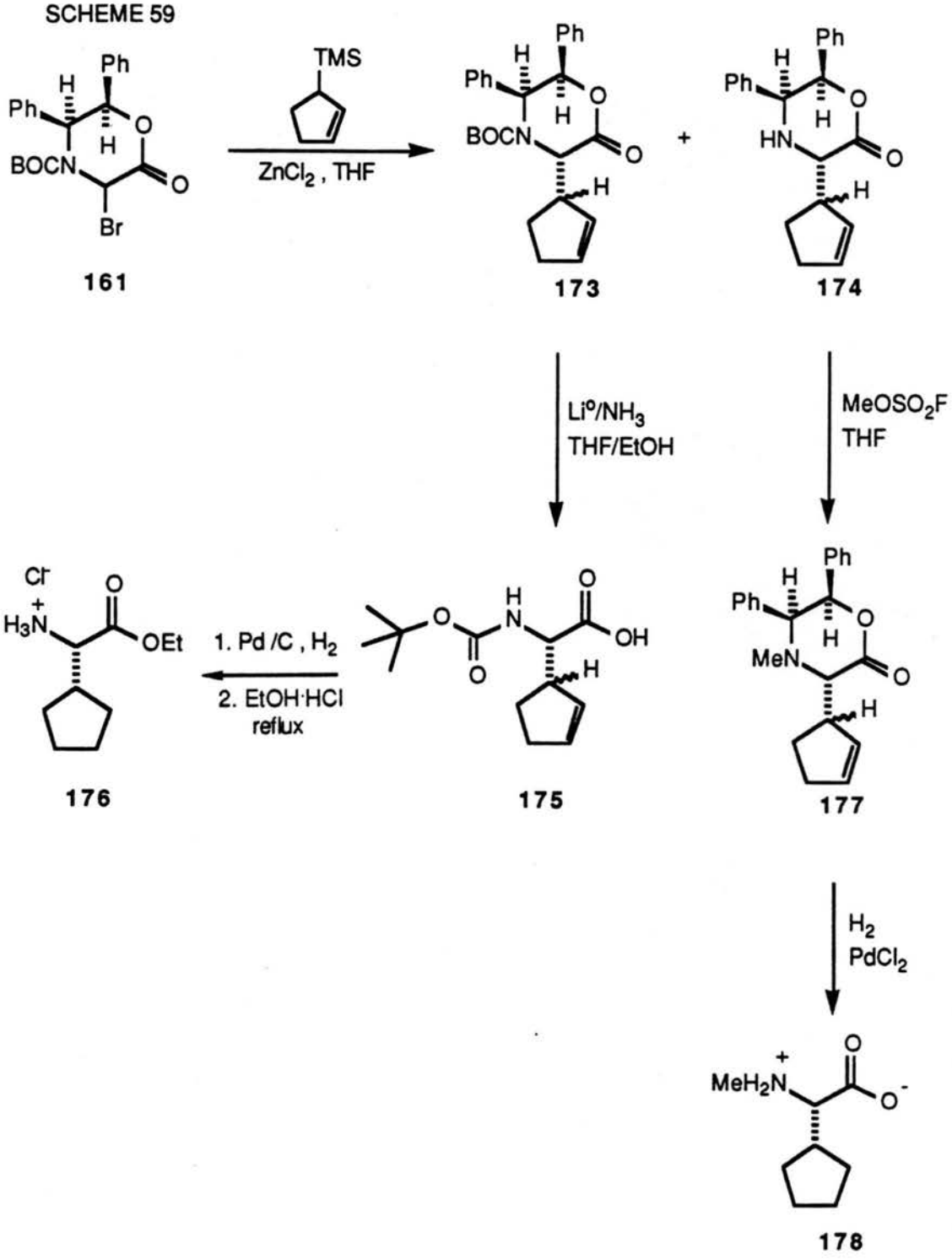
A straightforward two-step synthesis of **165** was envisaged involving the preparation and subsequent dissolving metal deprotection of oxazinone **170**. Bromoglycinate **132** was coupled to commercially available 3-(trimethylsilyl)-1-cyclopentene ($ZnCl_2$, THF) to give **170** in 82% yield as a 1:1 mixture of diastereomers. The diastereomers proved inseparable and the mixture was deprotected by lithium/liquid ammonia reduction to afford **165** as a diastereomeric mixture (Scheme 58). Hydrogenation of **170** gave the saturated amino acid cyclopentylglycine **171** which was ≥95% enantiomerically pure. Hydrogenation of cyclopentenylglycine also afforded **171** which again proved to be nearly enantiomerically pure. It could therefore be concluded that the C2 stereogenic center was stereochemically pure and that the diastereomeric mixture arose from the presence of epimers at the 2'-carbon. Acylation of cyclopentylglycine and comparison of the rotation to literature values established the stereochemistry of the 2-carbon to be (S). The synthesis therefore resulted in the preparation of a mixture of diastereomers of cyclopentenylglycine having the (2S,2'R) and (2S, 2'S) configurations. It is interesting to note that cyclopentenyl glycine occurrs in nature as this same mixture of diastereomers. Only the (2S,2'R) diastereomer is biologically active.[49] It is also worth noting that cyclopentyl glycine **171** is itself biologically active, being a competitive inhibitor of isoleucine uptake in *E. coli*.[50]

SCHEME 58



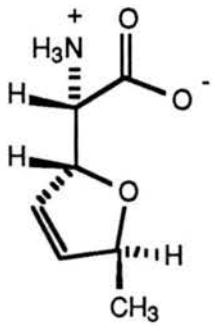
The t-BOC protected cyclopentenyl glycine was prepared in an analogous fashion. Coupling of the 3-(trimethylsilyl)-2-cyclopentene to bromoglycinate **161** gave the desired oxazinone **173**, again as a mixture of diastereomers, plus the free amine **174** (Scheme 59). Dissolving metal reduction of **173** gave the t-BOC protected amino acid in 70% yield. Stereochemical analysis of the cyclopentylglycine ethyl ester **176** obtained from **175** showed the amino acid was obtained ≥96% enantiomerically pure at the 2-carbon. It is worth noting here that the t-BOC protected oxazinones may be valuable precursors for the synthesis of N-alkyl α-amino acids. While no systematic study has been carried out, oxazinone **174** was treated with methyl fluorosulfonate in THF to give the methylated derivative **177** by ^{1}H NMR. Hydrogenation gave the corresponding N-methylcyclopentyl glycine **178**.

SCHEME 59


Ph
H
Ph
O
H
BOCN
O
Br
161
TMS
ZnCl2 , THF
Ph
H
Ph
O
H
BOCN
O
H
173
+
Ph
H
Ph
O
H
HN
O
H
174
Li°/NH3
THF/EtOH
MeOSO2F
THF
Cl-
+
H3N
O
OEt
176
1. Pd /C , H2
2. EtOH·HCl
reflux
H
N
O
O
OH
O
H
175
Ph
H
Ph
O
H
MeN
O
H
177
H2
PdCl2
+
MeH2N
O
O-
178

Furanomycin

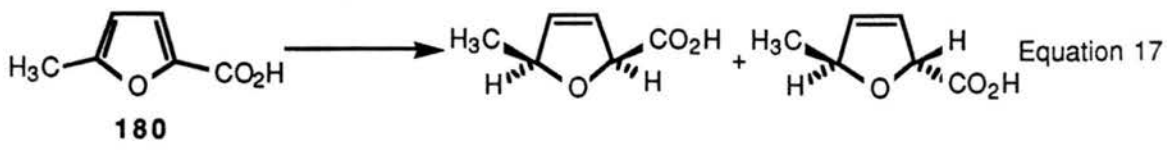
Furanomycin **179** is an antibiotic amino acid isolated from culture filtrates of *Streptomyces threomyceticus*.[51] It is a growth inhibitor of *E. coli* and believed to be a competitive antagonist of L-isoleucine.[51] The amino acid contains a 5'-methyl-2',5'-dihydrofuran moiety and the absolute configuration was determined by x-ray analysis[52] and total synthesis[53] to be (2S,2'R,5'S).



Furanomycin

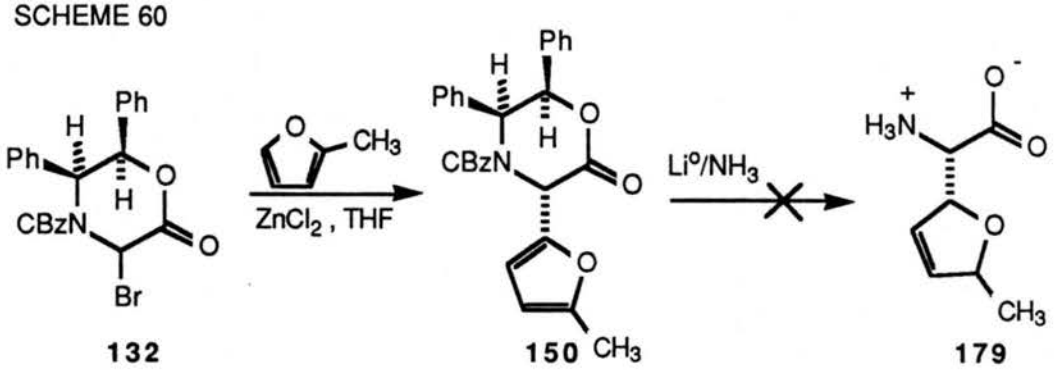
179

The obvious precursor to **179** is the (5'-methylfuryl) oxazinone **150**. The preparation of **150**, described earlier, was accomplished by treating a mixture of 5-methylfuran and bromoglycinate **132** with $ZnCl_2$. Since a Birch reduction on 5-methyl-2-furoic acid **180** was used successfully by Joullie and coworkers[53] in their synthesis of furanomycin (Equation 17), it was hoped that this type of reduction would cleave heterocycle **150** to give the free amino acid as well as reduce the furan ring to the corresponding 2,5-dihydro derivative (Scheme 60). Unfortunately, reduction of **150** failed, affording no isolable amino acids. The difficulty in this transformation can be attributed to the instability of the intermediate furyl anion **181** (Scheme 61). Alkyl furans are known[54] to undergo ring opening under Birch reduction conditions (path a). The furoic acids are more readily reduced to the 2,5-dihydro compounds due to the stabilization of anion **178** by the carboxylate group (path b).

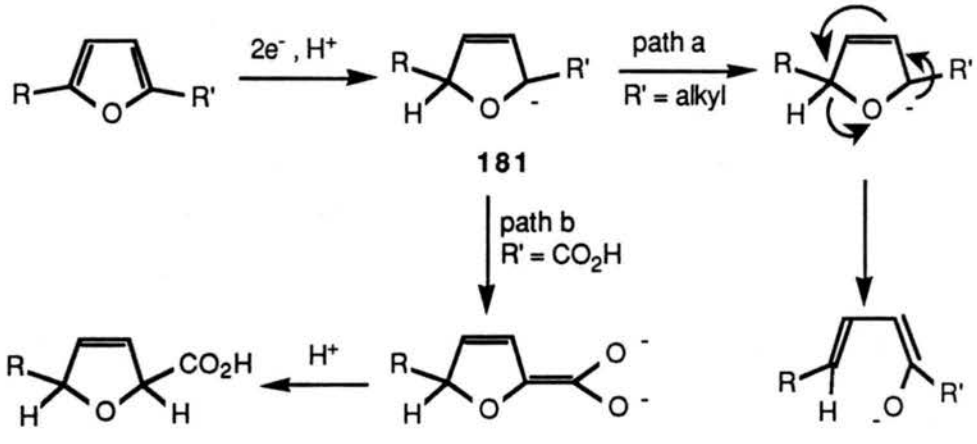


Equation 17

SCHEME 60



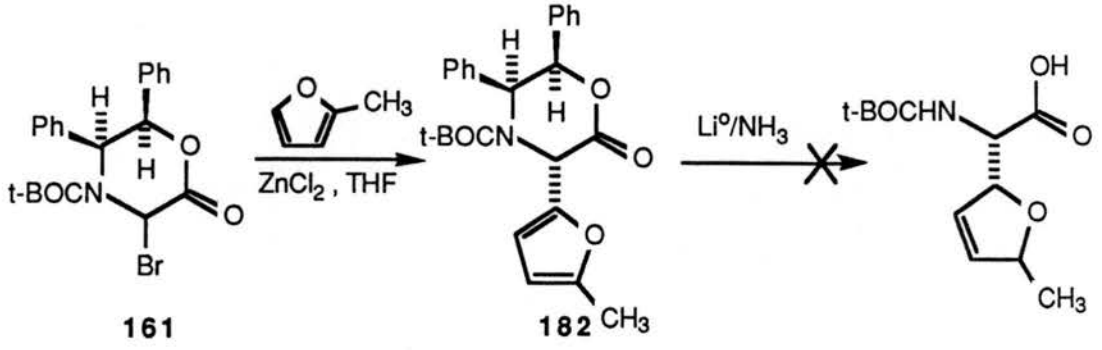
SCHEME 61



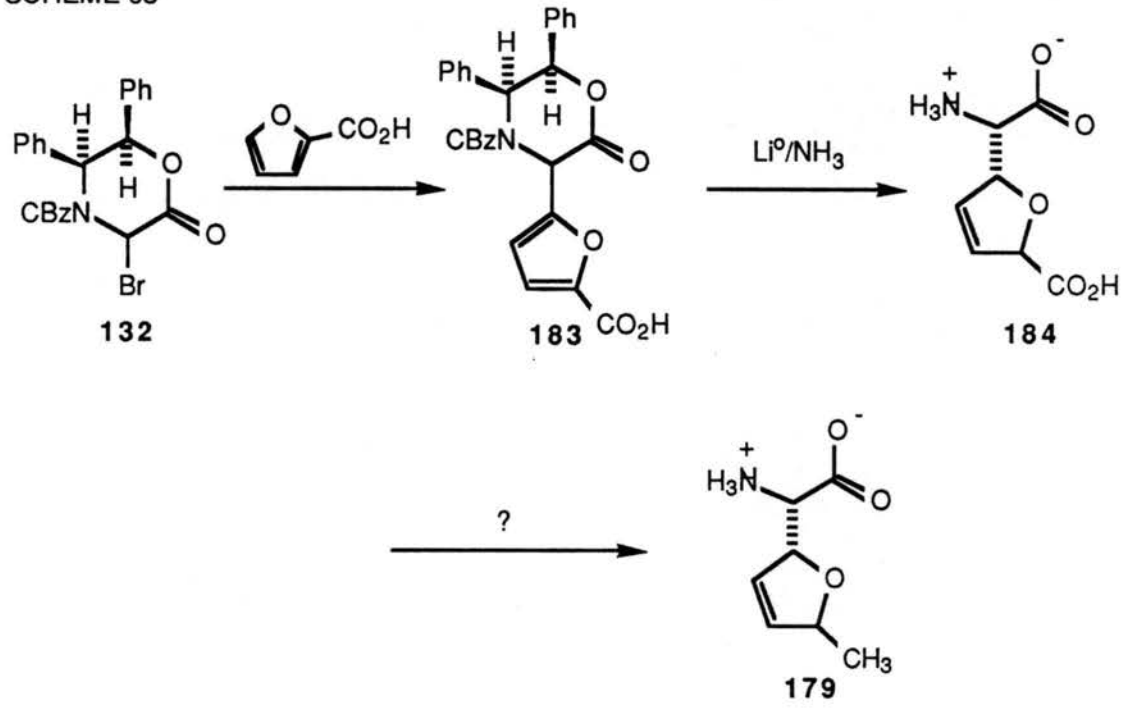
In the hope that deprotection could be achieved prior to ring cleavage the t-BOC derivative **182** was prepared. Again, dissolving metal reduction resulted only in decomposition of the starting material (Scheme 62). A route to furanomycin can be envisaged that involves coupling of 2-furoic acid to bromoglycinate **132** followed by Birch

reduction to afford the 2',5'-dihydro derivative **181**. However, the problem of selectively reducing one carboxylic group to a methyl group would remain (Scheme 63).

SCHEME 62



SCHEME 63

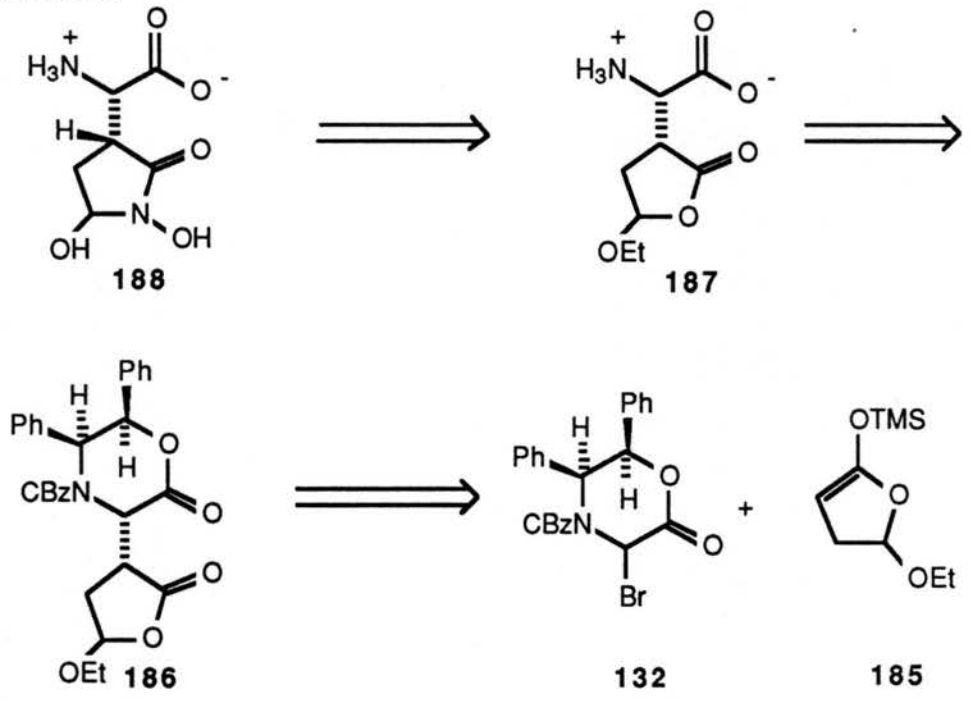


Dealanylalahopcin

Dealanylalahopcin **188** is a naturally occurring antibiotic amino acid isolated from *Streptomyces albulus* subsp. *ochragerus*.[55,56] As a peptide with alanine (Alahopcin) it shows antibiotic activity, collagen prolylhydrolase inhibition, and a stimulatory effect on the production of humeral immune response to bacterial α-amylase in mice.[57]

Dealanylalahopcin alone shows collagen prolylhydrolase inhibition and is weakly antibiotic.[55] The amino acid contains an interesting N-hydroxy succinimide semialdehyde moiety. The retrosynthetic analysis is shown in Scheme 64. It was reasoned that the silyl ketene acetal of γ-ethoxy butyrolactone **185** could be coupled to bromoglycinate **132**. Deprotection would give the corresponding amino acids having the requisite number of carbons in the proper oxidation state. Treatment with hydroxylamine would furnish **188**. The hydroxamic acid functionality was not to be prepared at the oxazinone stage because the N-O bond was not likely to survive the reductive deprotection.

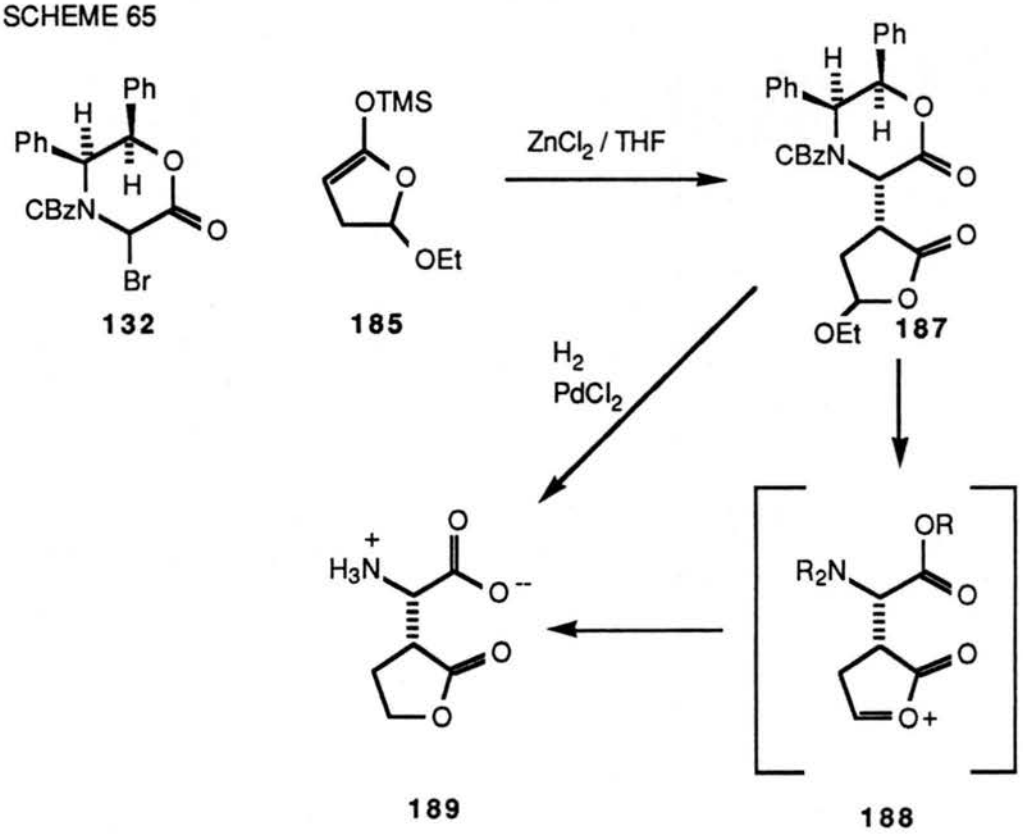
SCHEME 64



γ-Ethoxybutyrolactone was synthesized according to the procedure of Wermuth,[58] and subsequently converted to the silyl ketene acetal **185** by standard transformation. Coupling of **185** to the bromoglycinate was carried out (THF, $ZnCl_2$) to afford the corresponding homologated heterocycle **186** as a mixture of at least three diastereomers, the configurations of which have not been determined (Scheme 65). Unfortunately oxazinone **186** could not be hydrogenated readily to give **187**. Several attempts at

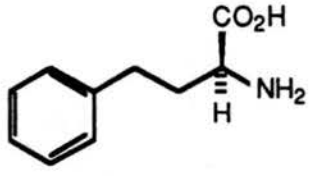
deprotection were made but the reactions were very messy affording little identifiable material. One product that was isolated was the butyrolactonyl glycine **189** which presumably arises by reduction of the transient oxonium ion **187** formed in the slightly acidic reaction medium. Attempting the Birch type reduction was the next logical step. A primary concern was that the butyrolactone moiety of **184** would undergo ammoniolysis but it was encouraging to see the γ-ethoxybutyrolactone could be recovered unchanged from a liquid ammonia solution. Unfortunately, the Birch reduction failed in all attempts; no amino acids were isolated. Work on this synthesis was suspended at this time because other lines of research were of higher priority. However, it is probable that the deprotection can be effected by hydrogenation in a neutral or slightly basic medium.

SCHEME 65

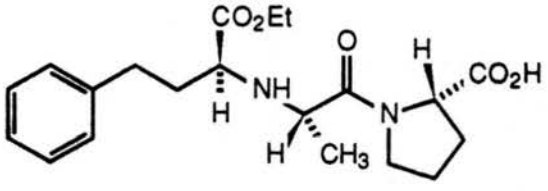


Homophenylalanine and 4-Methoxyhomophenylalanine

Homophenylalanine **142** is an unnatural amino acid, the structure of which can be found in a number of pharmacologically important compounds,[59] most notably the antihypertensive Enalipril **190** developed by workers at Merck, Sharp & Dohme, Inc. The synthesis of **142**, presented at the beginning of this chapter, simply involves coupling of the silyl enol ether of acetophenone **140** to the electrophilic glycinate **132** to give oxazinone **141** (Scheme 66). Coupling in THF gives a 7:1 mixture of diastereomers while carrying out the coupling reaction in acetonitrile gives **141** as a 14.5:1 mixture of diastereomers. In each case the anti diastereomer predominates. A single recrystallization followed by hydrogenolysis afforded L-homophenylalanine **142** in ≥95% ee.

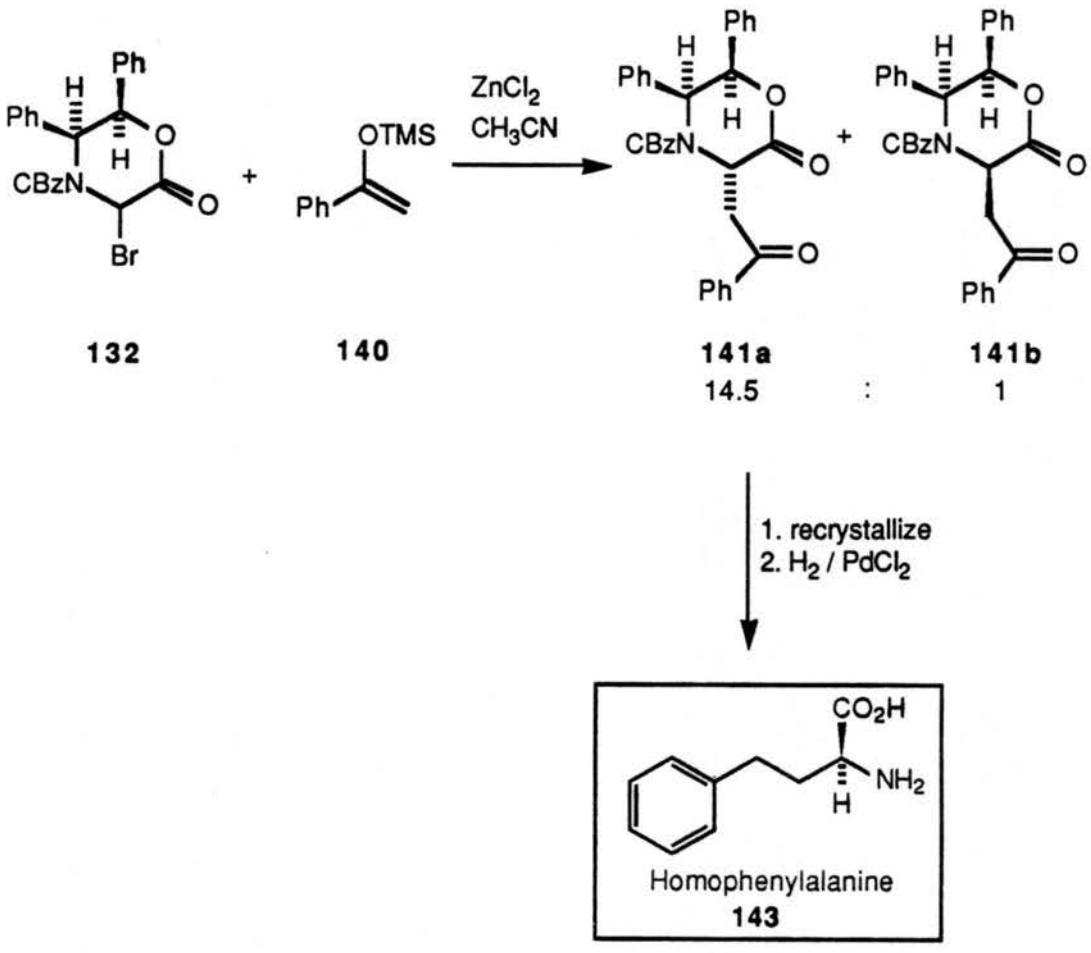


143



Enalipril
190

SCHEME 66



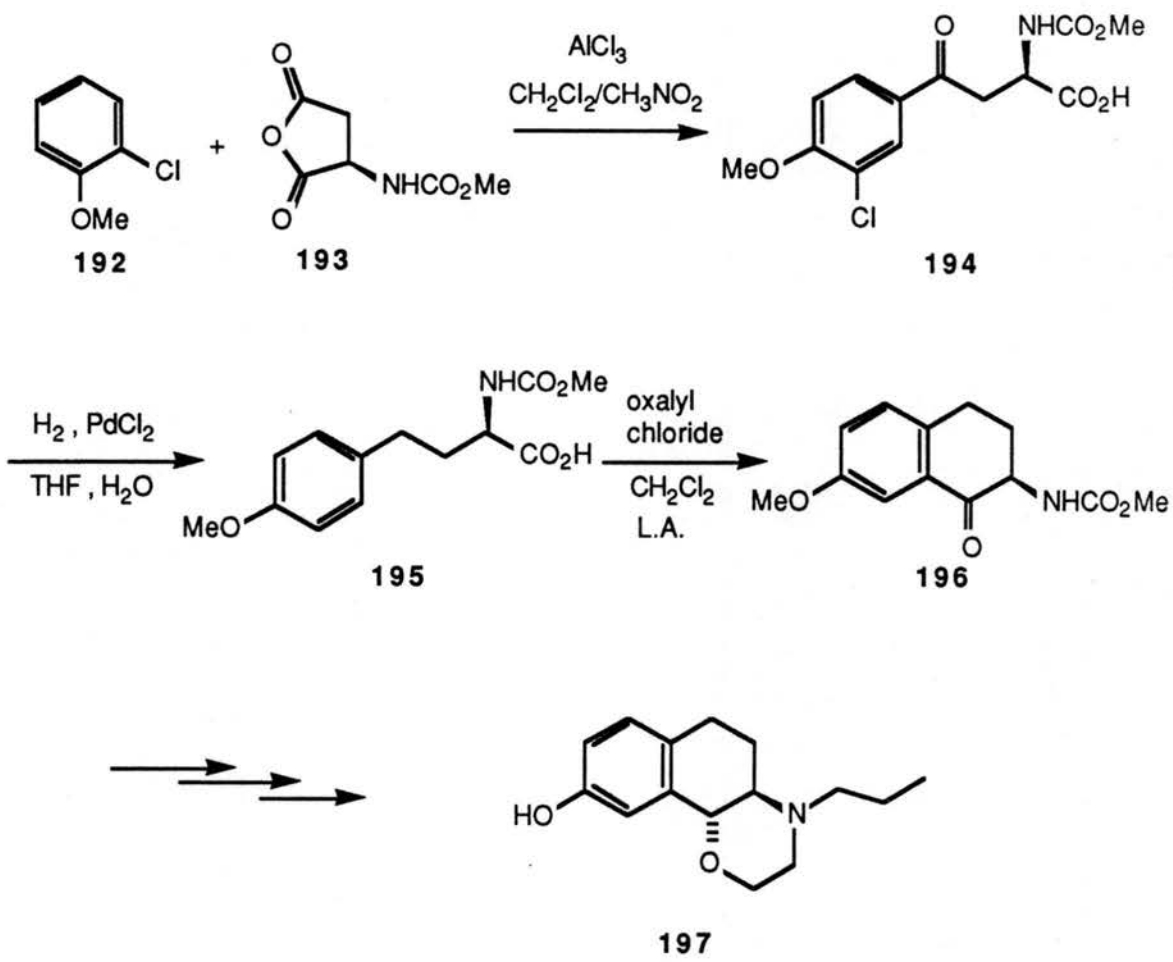
132 **140** **141a** : **141b**

14.5 : 1

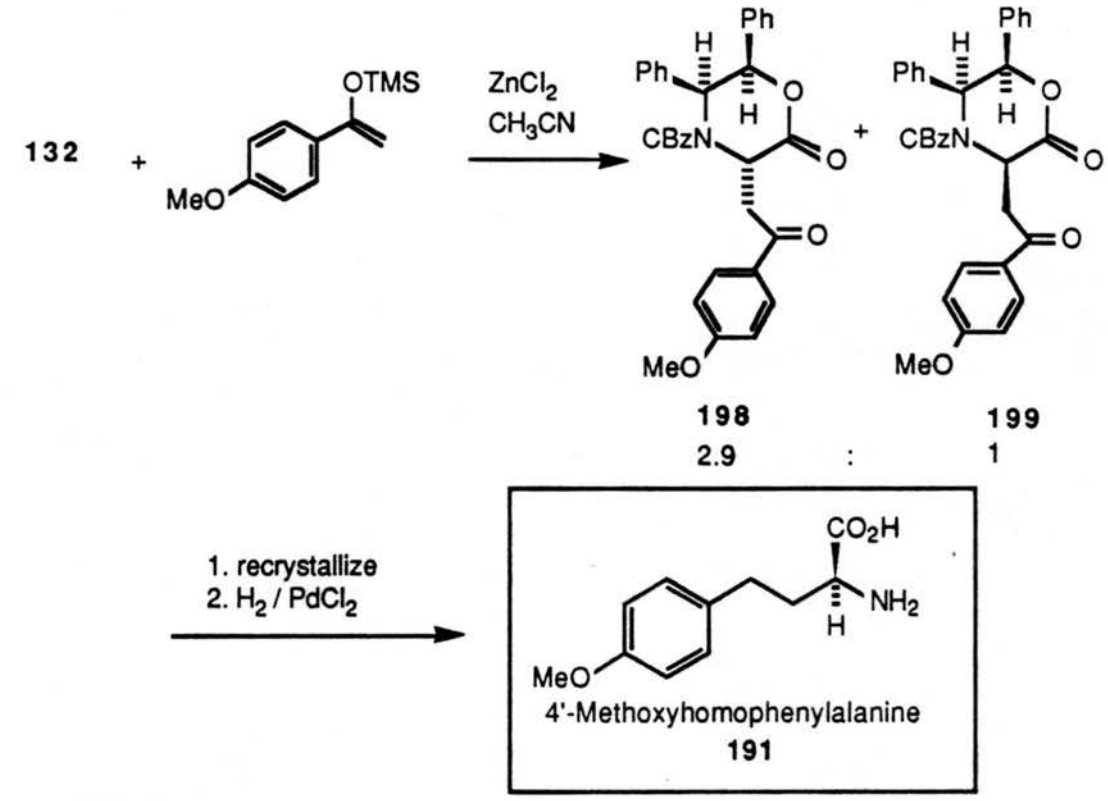
4'-Methoxyhomophenylalanine **191** is another unnatural amino acid that has been incorporated into a compound of pharmacological interest. This amino acid has also been prepared by workers at Merck, Sharp and Dohme, Inc. by a Friedel-Crafts acylation of 2-chloroanisol **192** followed by hydrogenation (Scheme 67).[61] The protected 4-methoxy homophenylalanine **194** was then cyclized in a second Friedel-Crafts acylation to give **196**. Subsequent steps provided the tricyclic oxazine **197** which has proven to be a potent dopamine agonist.[61] 4'-Methoxyhomophenylalanine **191** was prepared in a manner exactly analogous to homophenylalanine. Coupling of the trimethylsilyl enol ether of 4-methoxyacetophenone to **132** in acetonitrile gave oxazinones **198, 199** as a 2.9:1 mixture

of diastereomers. Recrystallization followed by hydrogenolysis gave enantiomerically pure **191** (Scheme 68).

SCHEME 67



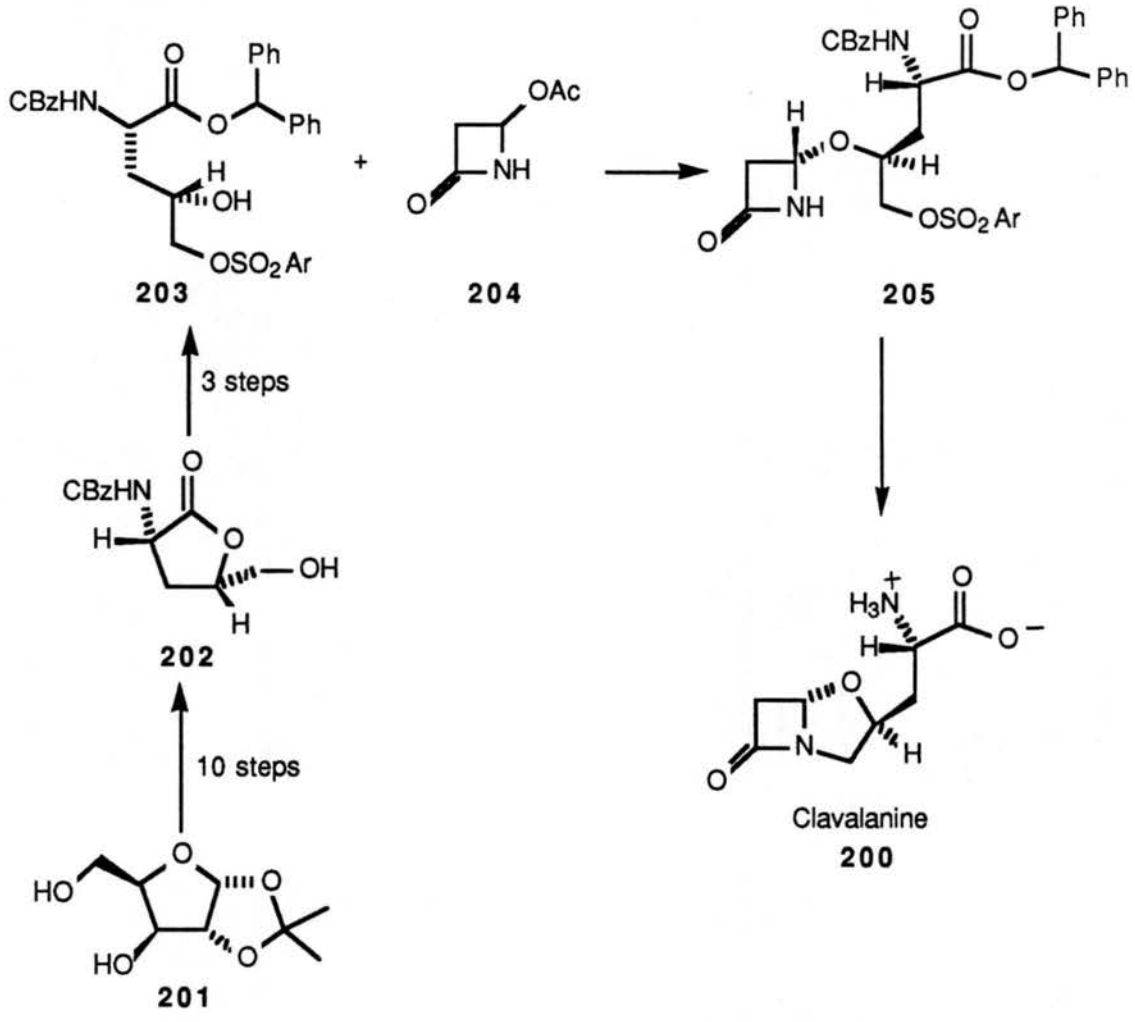
SCHEME 68



Clavalanine

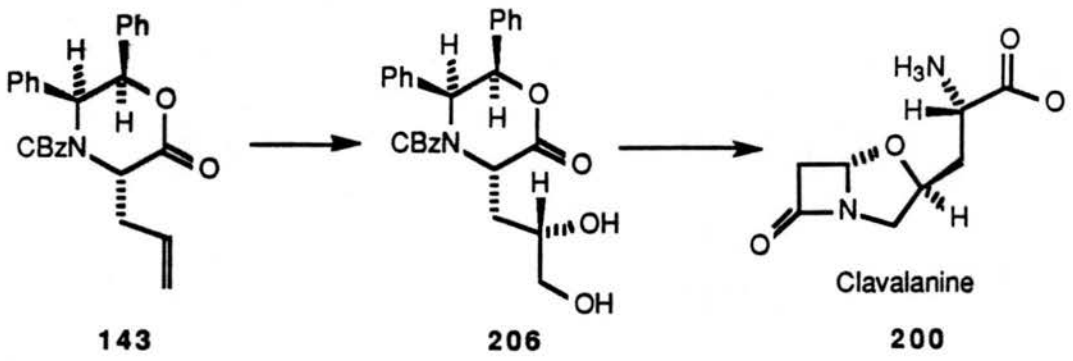
Clavalanine (Ro 22-5417) **200** is a clavam antibiotic isolated from *Streptomyces clavuligerus* by workers at Hoffmann La-Roche, Inc.[62] This β-lactam antibiotic is notable in that it is an antimetabolite of O-succinyl homoserine and intervenes in methionine biosynthesis.[62a] Most β-lactam antibiotics inhibit cell wall biosynthesis. A stereorational approach to clavalanine was reported by Weigele and coworkers[63] that involves the coupling of the protected 6-p-chlorophenylsulfonate ester of (2S,4S)-dihydroxynorvaline **203** with 4-acetoxyazetidinone **204** (Scheme 69). The key intermediate **203** was obtained via a 13 step synthesis from the D-xylose derivative **201**.

SCHEME 69



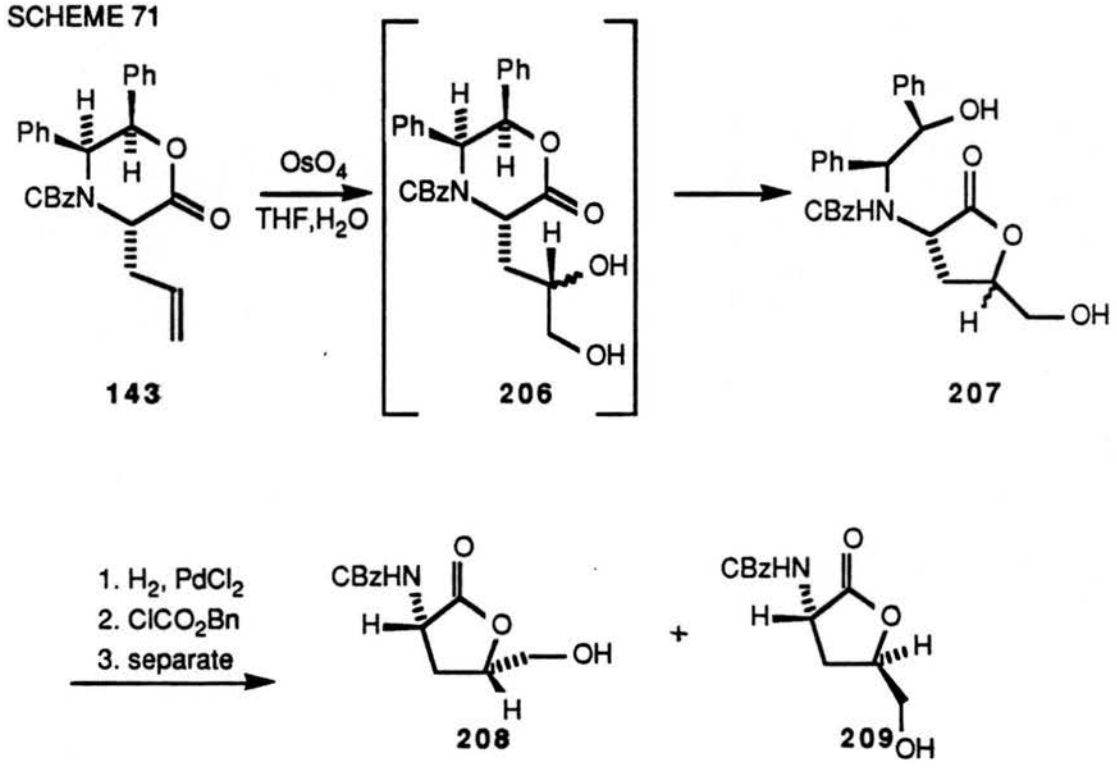
Oxidation of the allylic side chain of oxazinone **143** should provide a facile, two step synthesis of the protected dihydroxynorvaline **206**. The protected amino acid could then be employed in the synthesis of clavalanine utilizing the conversions developed by Weigele, et al. (Scheme 70).

SCHEME 70



Oxidation of **143** with osmium tetroxide resulted in the cis hydroxylation of the olefin but afforded only the δ-lactone **207** as a 1:1 mixture of diastereomers epimeric at C4 (Scheme 71). The mixture of lactones was hydrogenated, acylated, and separated to furnish the N-protected amino lactones **208** and **209**. Lactone **208** proved to be identical (by ^{1}H NMR and $[\alpha]_D$ at similar concentration) to the Roche intermediate **202**[64] obtained in 10 steps from xylose derivative **201**.

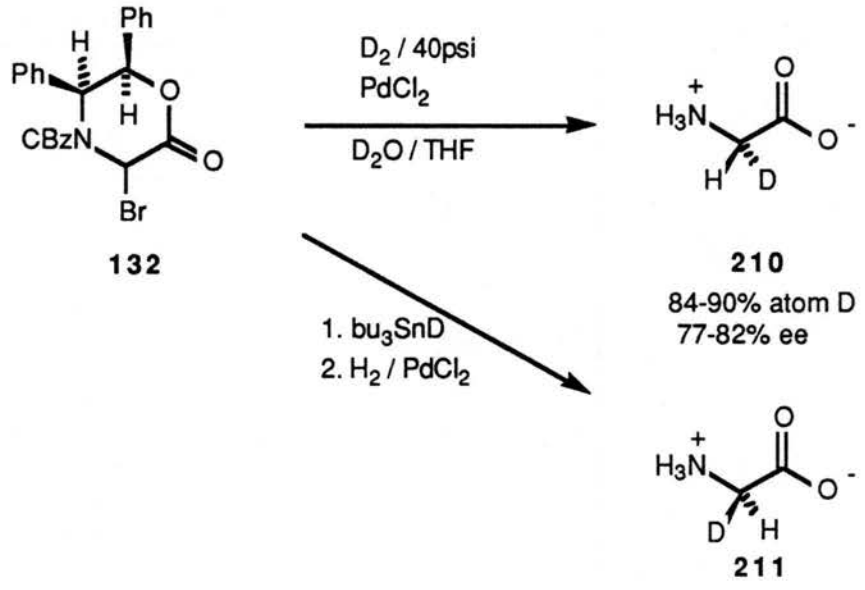
SCHEME 71



Chiral Glycine

Chiral glycine[65] has become an increasingly important substance for the study of numerous biochemical reactions and serves as a starting material for stereospecific conversions into other important labeled compounds such as chiral acetic[66] and chiral glycolic acid.[67] A number of syntheses have been reported that involve tedious multistep sequences from enantiomerically pure starting materials or employ somewhat capricious enzymatic conversions. Bromoglycinate **132** has been found to cleanly undergoe deuteration (D_2, $PdCl_2$) to give (S)-[2-$^2H_1$]glycine **210** in 51-54% yield with 84-90% enantiomeric excess (Scheme 72). It is curious to note that reduction of **132** with Bu_3SnD followed by hydrogenolysis affords (R)-[2-$^2H_1$]glycine **211** in 60% ee (i.e. the reverse stereochemical outcome from the D_2 reduction).

SCHEME 72

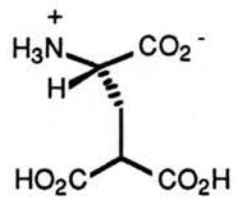


Although the optical purity of the chiral glycine obtained is slightly lower than that reported previously, the relatively high overall chemical yield and experimental simplicity of the synthesis make it a practical alternative to the more tedious approaches. Furthermore, since the isotope is introduced in the last transformation, this methodology should be particularly suited to the synthesis of [2-$^3H_1$]glycine.

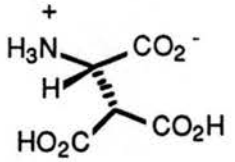
β-Carboxy Aspartic Acid

γ-Carboxyglutamic acid (Gla) **212** is a biologically important amino acid formed by vitamin K mediated γ-carboxylation of glutamyl residues in blood coagulating proteins.[69] The γ-carboxyl groups are essential for calcium binding and blood coagulation. β-Carboxy aspartic acid (Asa) **213** is the lower homologue of Gla and has been identified in *E. coli* ribosomal extracts[70] and, more recently, in human atherosclerotic plaque.[71] Asa is the most acidic natural amino acid known (first pKa ~0.2) and exists with the β-carboxyl zwitterion being four times more prevalent than the α-carboxyl zwitterion.[72] An x-ray analysis of Asa suggests the β-carboxyl group is partially ionized even in the solid state.[72]

β-Carboxy aspartic acid is unstable in both acidic and basic media.[73] In acid, Asa readily decarboxylates to afford aspartic acid (Asp) **214** (Scheme 73). In base, ammonia is eliminated to give tricarboxyethylene **215**. Above pH = 12 the amine group is not protonated and is therefore a poor leaving group. As a consequence, Asa is stable at high pH (≥12).

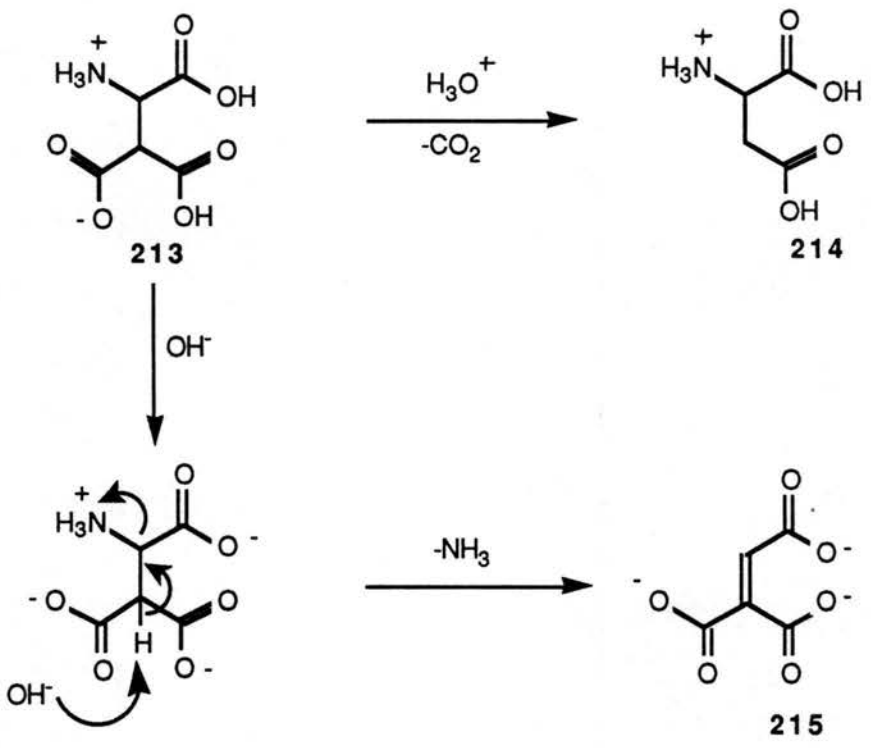


γ-carboxyglutamic acid
212



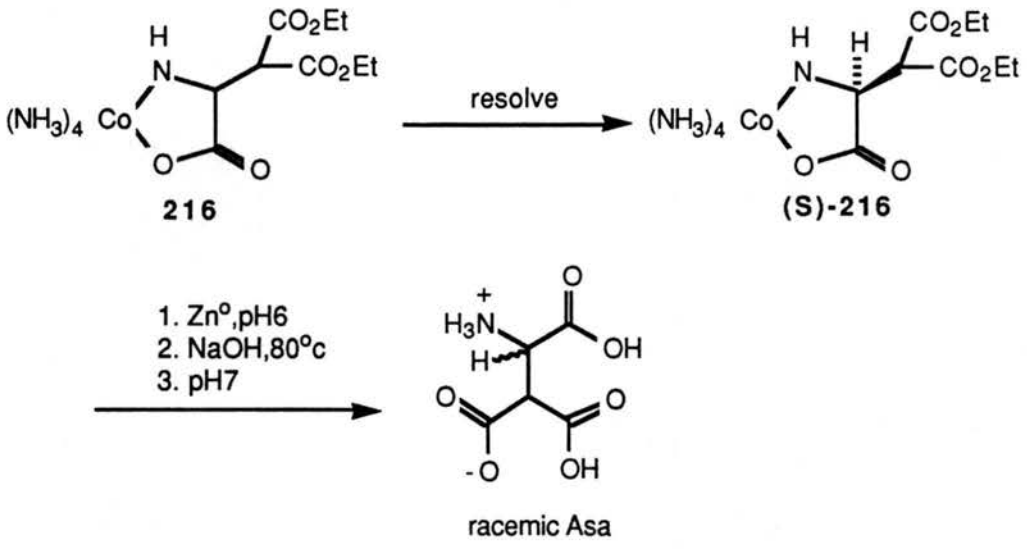
β-carboxyaspartic acid
213

SCHEME 73



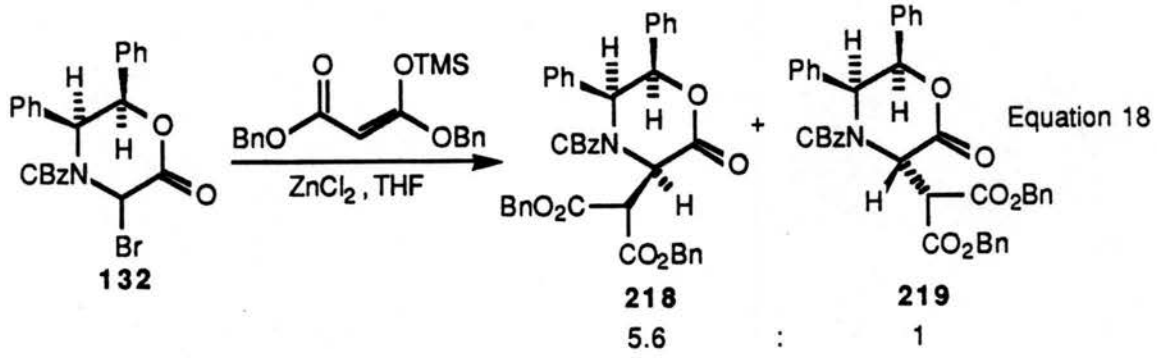
As a result of the chemical reactivity of Asa the synthesis of this structurally simple molecule has been challenging. To date there have been a number of syntheses of racemic Asa reported.[74] While one synthesis of the optically active trimethylester of β-carboxy aspartic acid has been devised,[36] the preparation or isolation of enantiomerically pure Asa as the free amino acid zwitterion has not been achieved. Sargeson and Dixon reported[75] the synthesis and resolution of the [(diethyl-β-carboxyaspartato)tetraamminecobalt(III)]$^{2++}$ ions **216**. However, reduction and alkaline hydrolysis of the cobalt complex results in complete racemization of the Asa (Scheme 74).

SCHEME 74

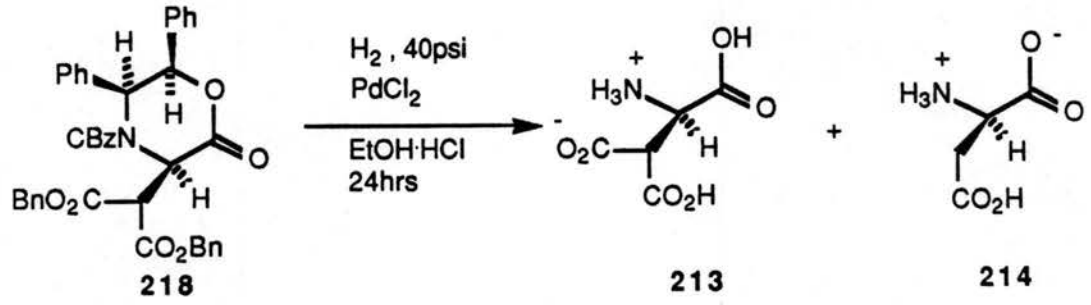


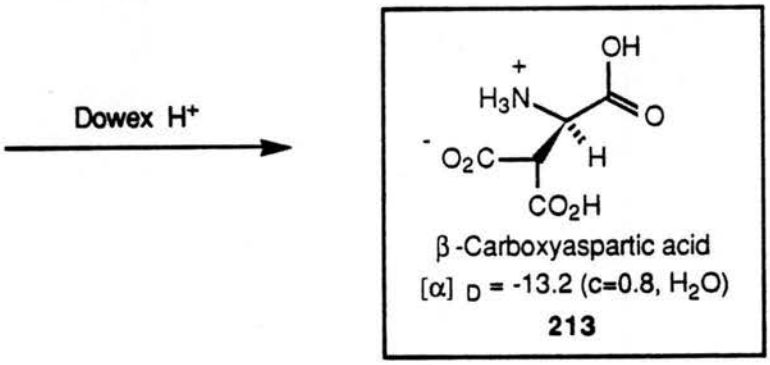
The amino acid synthesis described herein was believed to be ideally suited for the preparation of optically pure Asa and would allow isolation of the zwitterion with minimal manipulation. Bromoglycinate **132** was reacted with the trimethylsilyl ketene acetal of dibenzyl malonate **217** to give the homologated heterocycle in 53% yield as a 5.6:1 mixture of diasteroemers **218, 219** with the syn compound **218** predominating (Equation 18). The diastereomeric oxazinones were separated readily by HPLC to give pure **218** and **219**. The syn diastereomer **218** was hydrogenated ($PdCl_2$, 40 psi, 24 hr) and worked up as usual (filter, concentrate, triturate with Et_2O) to give a mixture of Asa and Asp (Scheme 75). The unfortunate formation of Asp can be attributed to the acidic reaction medium and relatively long reaction times. In order to separate the two amino acids, the extremely low pKa of Asa was exploited. Stirring an aqueous solution of the two amino acids with acidic ion exchange resin (Dowex-50W-X8 H^+ form) resulted in selective retention of aspartic acid. Decanting the supernatent, removing the trace organics by passing through a C18 filter (Millipore SEPPAK C18 cartridge) and concentrating in vacuo afforded (D)-β-carboxy aspartic acid hydrochloride monohydrate in 30% yield from **218**. The amino acid displayed an optical rotation: $[\alpha]_D$ = -13.2 (c = 0.8, H_2O). ^1H NMR analysis (D_2O) showed the characteristic singlet for Asa and trace amounts of Asp. Decarboxylation and

esterification (EtOH·HCl, reflux) gave diethylaspartate HCl, which was converted to the mosher amide and analyzed by ^{19}F NMR. The analysis showed the amino acid was prepared in ≥98% e.e. The first synthesis of enantiomerically pure β-carboxy aspartic acid had been achieved!



SCHEME 75

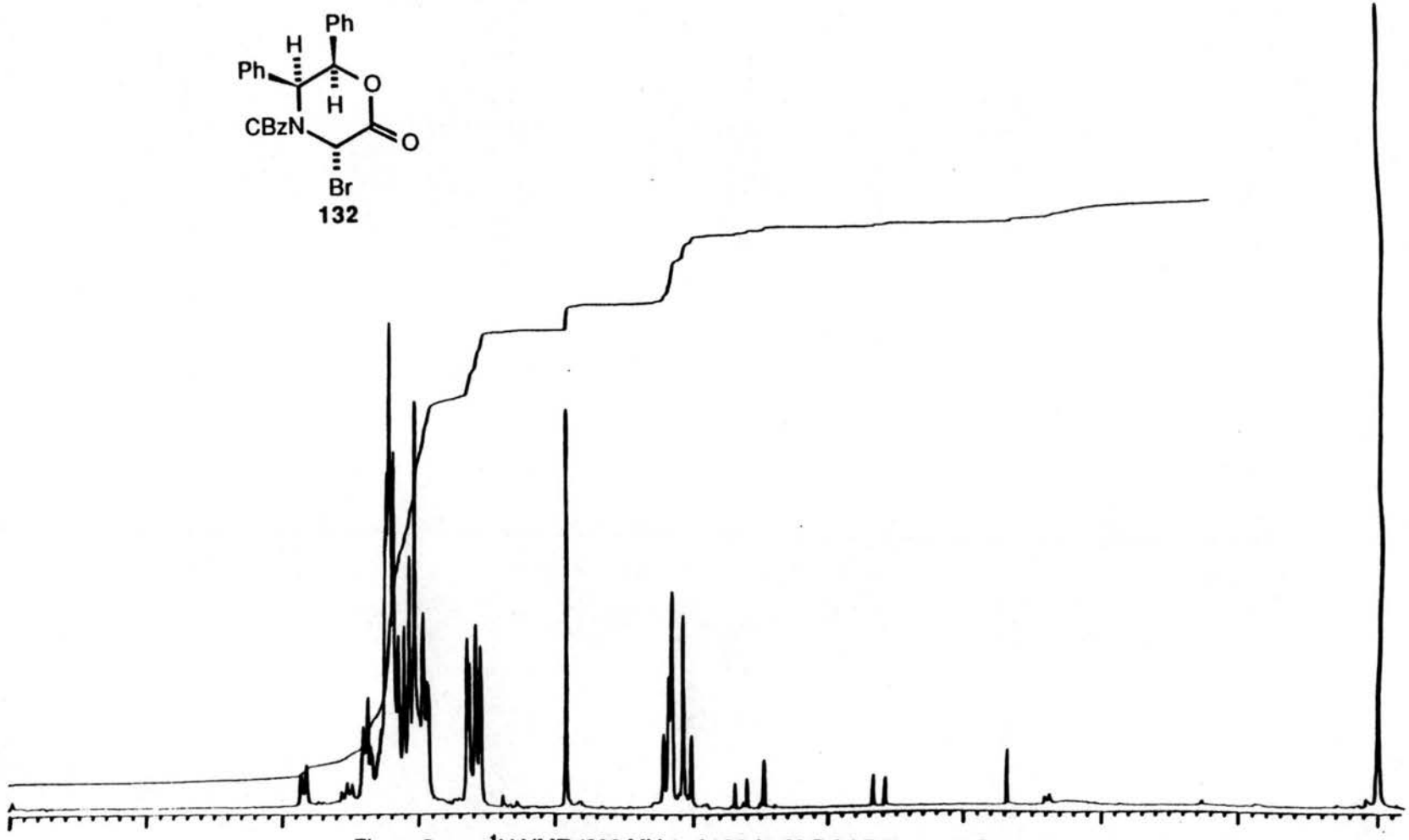




Mechanism and High Temperature NMR Studies

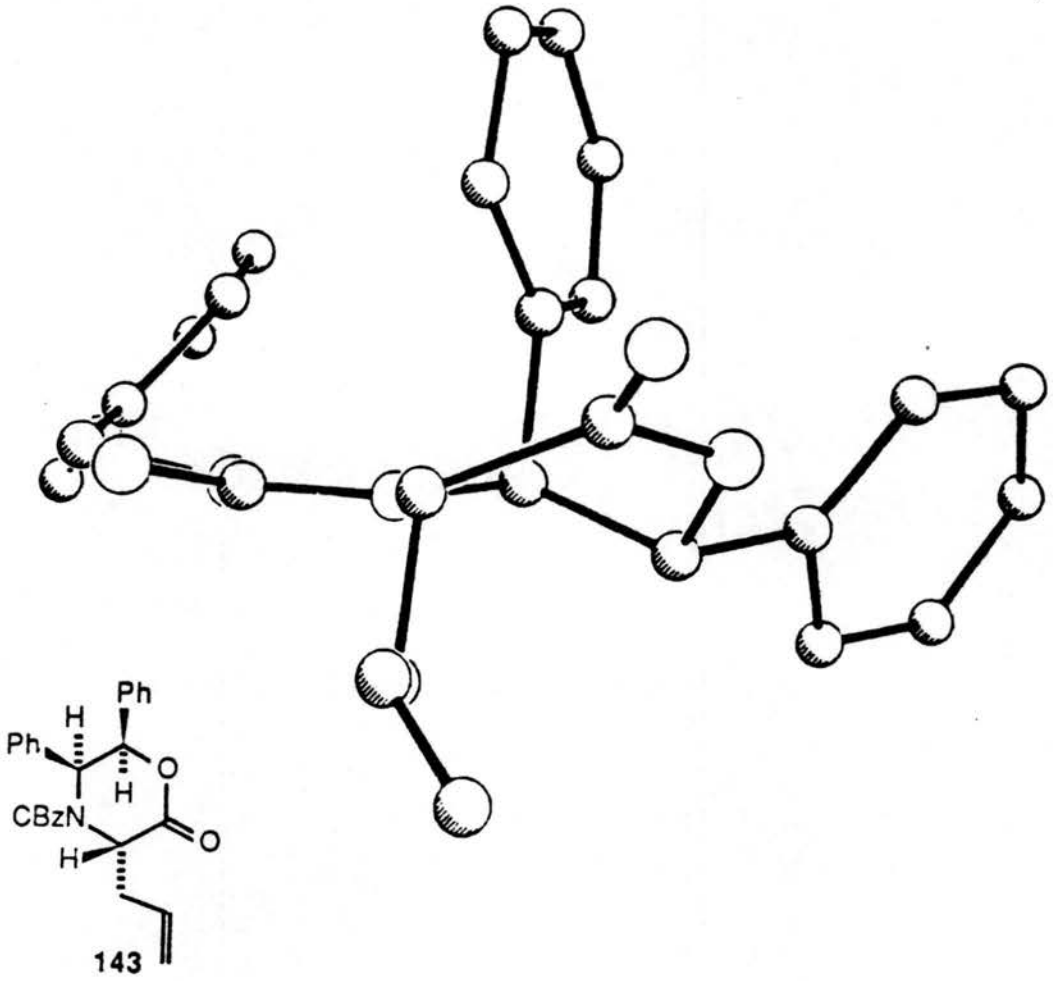
It can be seen that some reagents couple with bromoglycinate **132** to afford one diastereomer almost exclusively while others couple with little selectivity. Furthermore, the predominant diastereomer formed (syn or anti) is dependent upon the homologating reagent used. For example, the ethyl acetate silyl ketene acetal reacts with bromide **132** to give the syn diastereomer almost exclusively while allyltrimethylsilane couples with **132** to give only the anti product. In order to explain these results it is necessary to elucidate the mechanism of coupling. To do so, the stereochemistry of our starting bromoglycinate must be established. The bromide, like all of the N-protected oxazinones, gives an exceedingly uninformative ^{1}H NMR spectrum under normal conditions ($CDCl_3$, 25°C). Fortunately, high temperature ^{1}H NMR analysis can be carried out (120°C, $Cl_2DCCDCl_2$) and indicates that the bromide is obtained as a single diastereomer (Figure 8). Under the conditions employed for the preparation of **132** (NBS, CCl_4, reflux) one can reasonably expect to obtain the thermodynamically most stable compound. An x-ray structure of the allyloxazinone **143** (Figure 9) shows that this compound exists in the solid state in a twist boat conformation. In this conformation the C-5 phenyl ring is pseudo axial, the C-6 phenyl ring is pseudo equitorial, and the allyl group is anti to the phenyl rings and also in a pseudo axial position. It is always risky to draw conclusions about solution conformations based on crystal structures, nevertheless, since all of the alternate boat and chair forms of the anti compound (Structures B through E, Scheme 76) suffer from unfavorable diaxial and $A^{1,3}$ interactions,[76] conformation A (Scheme 76) is the least strained conformation and is believed to predominate in solution. Additionally, since all conformations of the syn coupled oxazinone (structures F through J, Scheme 77) are also subject to some unfavorable steric interactions the bromide will be formed as the thermodynamically more stable anti diastereomer.

It was initially envisaged that coupling would take place via electrophilic attack of imminium ion **133** on some reagent from the least hindered face of the molecule to give the



132

Figure 8 ^{1}H NMR (200 MHz) of **132** in $Cl_2DCCDCl_2$ at 393°K.

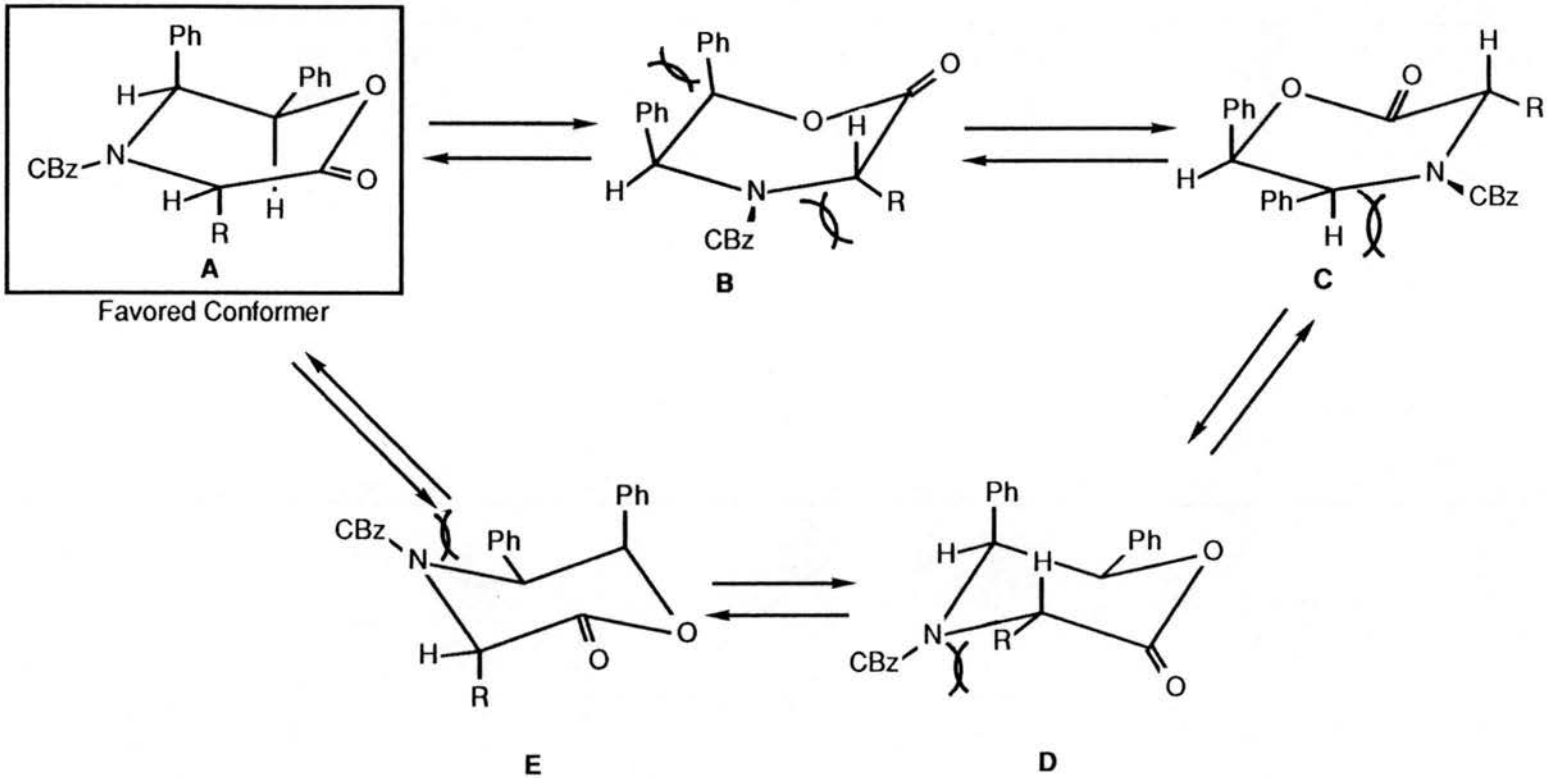


143

Figure 9 Stereostructure of **143**. Atoms are spheres of fixed arbitrary radius. Hydrogen atoms are not shown for clarity.

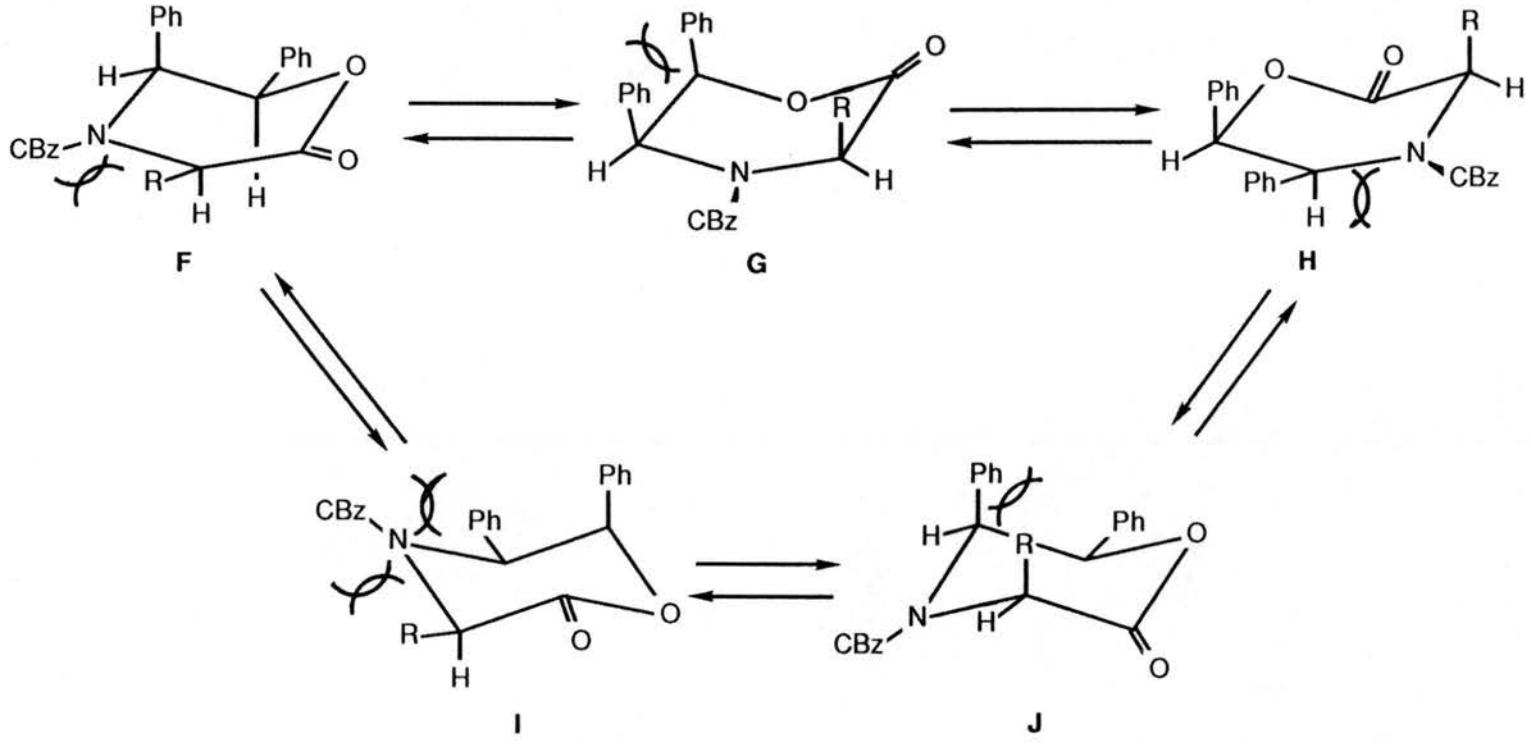
SCHEME 76

ANTI DIASTEREOMER



SCHEME 77

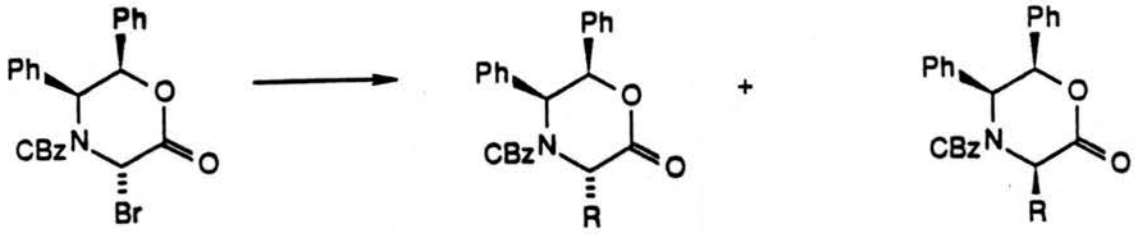
SYN DIASTEREOMER



anti diastereomer. The fact that one can observe good diastereoselectivity of coupling but from different sides of the oxazinone ring, depending upon the type of reagent employed, indicates that the coupling can take place by more than one mechanism. It is proposed that reagents of sufficient electron density at the attacking carbon (i.e., silyl ketene acetals) will couple to **132** via a Lewis acid (Zn^{++}) assisted S_N2 displacement of the bromide to give the syn diastereomer. Reagents having electron density at the attacking carbon that is insufficient to initiate S_N2 displacement of the bromide (i.e., allylsilanes) will undergo electrophilic attack by imminium ion **133** to give the anti diastereomer. The two pathways will compete when reagents of intermediate reactivity are employed to afford a diastereomeric mixture.

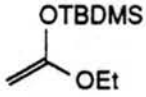
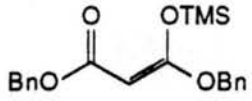
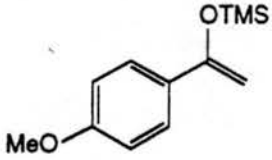
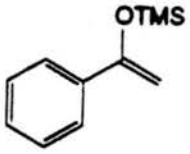
Table 3 lists a variety of reagents that have been coupled to bromoglycinate **132**, the conditions used in the coupling reaction, and the ratio of anti/syn diastereomers formed. The results outlined in Table 3 clearly show that for neutral reagents of considerable electron density at the attacking carbon (silyl ketene acetals, silylenol ethers) the use of a stronger Lewis acid (Ag^+) and/or more polar solvents, conditions that favor the S_N1 pathway, always increases the anti:syn diastereomeric ratio. Conversely, conditions that favor the S_N2 path (weaker Lewis acids and non-polar solvents) decrease the anti:syn diastereomeric ratio. While the experimental evidence strongly supports the proposed mechanism, the question of selectivity remains to be addressed; why do some reagents couple by one mechanism (almost) exclusively? In order to answer this question one more assumption must be made based on what has been discussed; namely, that bromide **132** is in the corresponding low energy conformation A at the time of coupling. In this conformation the carbon bearing the bromine atom is accessible to S_N2 attack, and the bromine-carbon bond is nearly parallel with the π-system of the urethane and is therefore conveniently positioned for imminium ion formation. Thus, conformation A allows ready coupling via both mechanisms.

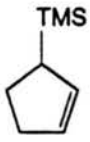
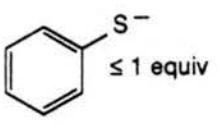
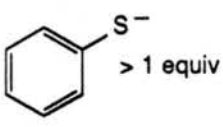
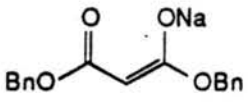
TABLE III



anti **syn**

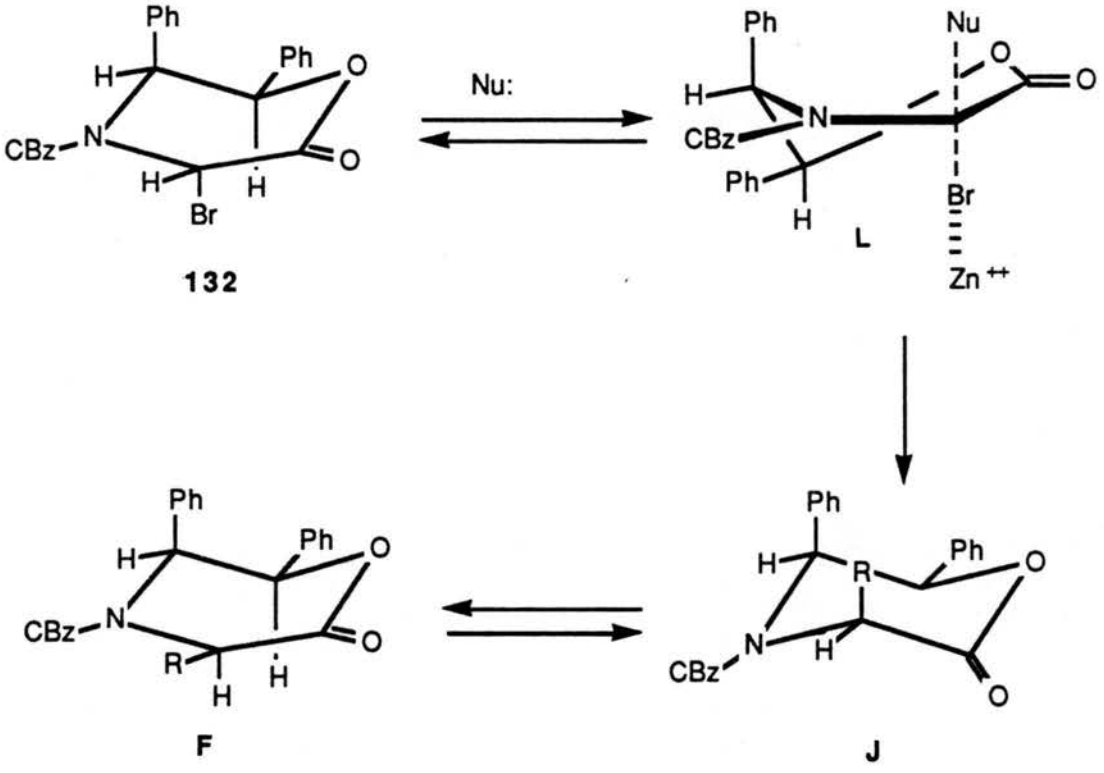
Coupling of Reagents to 132

ENTRY	REAGENT	SOLVENT	LEWIS ACID	RATIO ANTI/SYN
1		CH_2Cl_2	$ZnCl_2$	1:45
2	"	THF	$ZnCl_2$	1:14-45
3	"	THF	AgOTf	1:2
4		THF	$ZnCl_2$	5.6:1
5		CH_2Cl_2	$ZnCl_2$	1:11.2
6	"	THF	$ZnCl_2$	1:1.6
7	"	CH_3CN	$ZnCl_2$	2.9:1
8	"	THF	AgOTf	5.9:1
9		CH_2Cl_2	$ZnCl_2$	1:3.4
10	"	$CHCl_3$	$ZnCl_2$	1.4:1

ENTRY	REAGENT	SOLVENT	LEWIS ACID	RATIO ANTI/SYN
11	"	THF	$ZnCl_2$	7:1
12	"	CH_3CN	$ZnCl_2$	14.5:1
13	"	THF	AgOTf	24.5:1
14		THF	$ZnCl_2$	≥45:1
15	"	THF	AgOTf	≥45:1
16		THF	$ZnCl_2$	≥45:1
17		THF	—	minor/major
18		THF	—	≥98:2 only anti
19		THF	—	≥98:2
20	"	THF	—	≥98:2
21	CH_3ZnCl	THF	—	≥98:2
22	$Bu_2Cu(CN)Li_2$	THF/Et_2O	—	≥98:2

Nucleophilic (S_N2) displacement of the bromide proceeds through transition state L (Scheme 78). The nucleophile is relatively unencumbered at the start of attack but the molecule becomes progressively more crowded as the degree of carbon-carbon bond formation increases. The product is obtained initially in the chair conformation J having very unfavorable 1,3-diaxial interactions, and likely collapses to a less strained boat conformer.

SCHEME 78



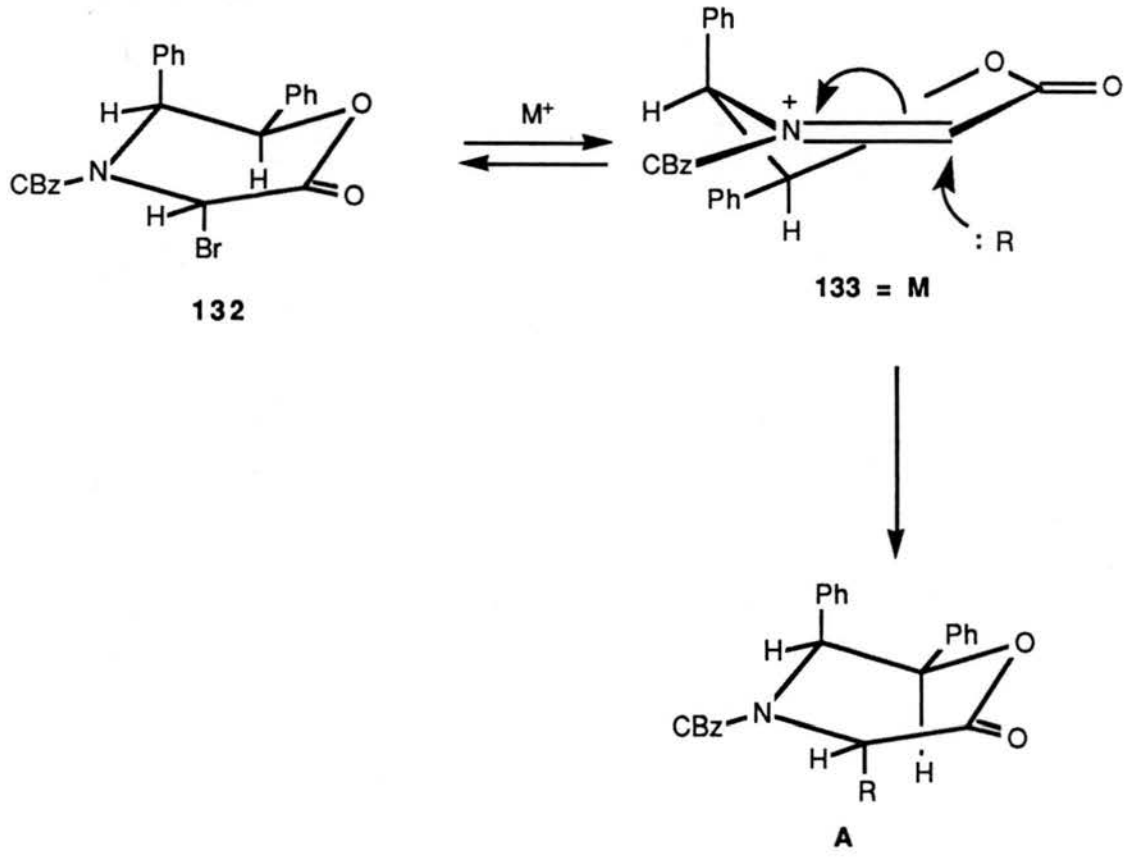
132 L

F J

In order for coupling to occur via the S_N1 pathway imminium M must be formed. Models show this ring to be severely strained and indicate that it is disposed to coupling from the bottom face (as shown in Scheme 79) for two reasons. First, in this strained conformation the top side of the heterocycle is effectively blocked by the C5 phenyl ring making approach of a reagent from this side difficult. Second, models clearly show that the transient imminium ion very closely resembles the thermodynamically most stable anti

diastereomer and formation of this product involves little more than the slight, and favorable, sp^2-sp^3 rehybridization of the α-carbon.

SCHEME 79



132

133 = M

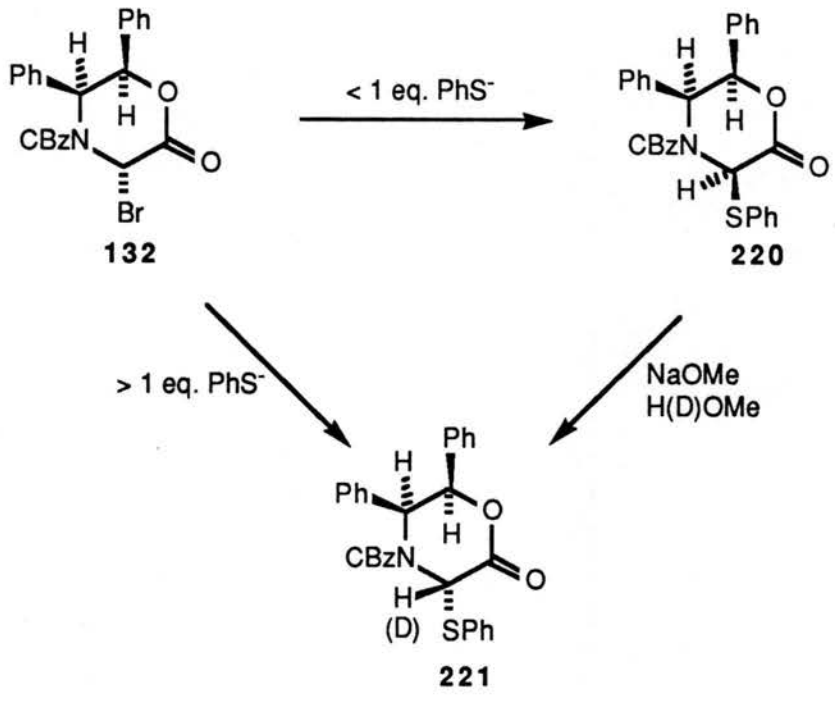
A

It is a reasonable estimation that both the transition state L and the imminium ion M are high energy species since both possess a highly strained oxazinone ring bearing three contiguous sp^2 centers, and that, of the two species, imminium ion M will be of higher energy since it is a charged molecule. All things being equal, a reagent would prefer to couple via the lower energy S_N2 pathway to give the syn diastereomer provided it is "nucleophilic" enough to overcome the considerable steric interactions present in the transition state. When the homologating reagent is not of sufficient electron density to couple via the S_N2 path the higher energy imminium ion must form. Coupling then takes place from the bottom side of the molecule to afford the anti diastereomer.

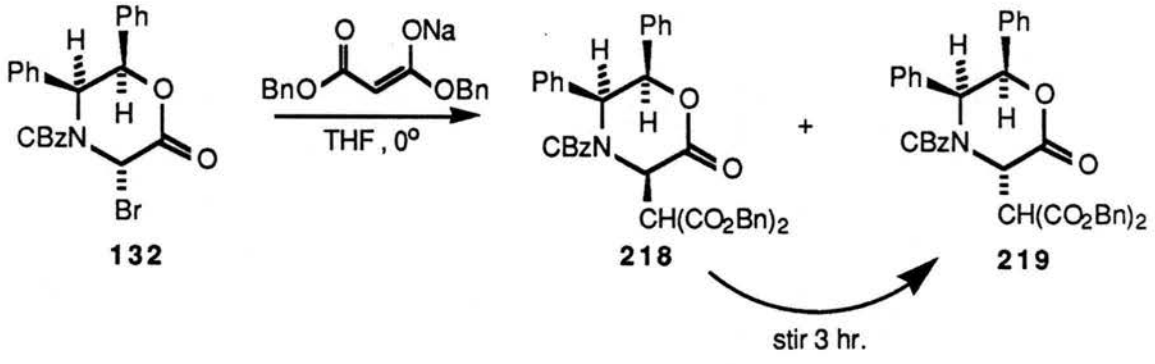
The observed kinetics for the coupling reactions also agree with our hypothesis. For the S_N2 pathway formation of transition state L should be rate limiting followed by collapse to starting materials or products. This should be a relatively rapid reaction. Indeed, coupling of the ethylacetate silyl ketene acetal to **132** in CH_2Cl_2 is complete in less than four minutes. For the S_N1 mechanism formation of the high energy imminium ion should be the rate limiting step and a slow process. In fact, coupling of allylsilanes to **132** takes place over several days. While these results are extremely qualitative, they do support the mechanistic interpretations.

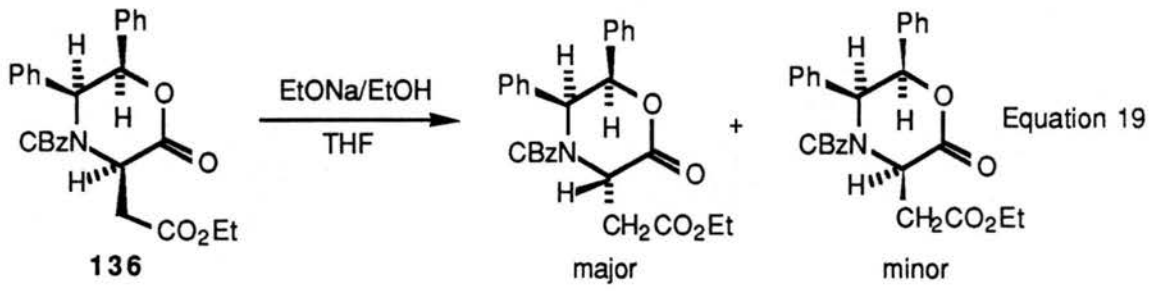
The rather interesting results obtained when basic nucleophiles are coupled to bromoglycinate **132** (Entries 17-20, Table 3) are also explained by the proposed mechanism. Sodium phenylthiolate when coupled to **132**, using less than one equivalent of the nucleophile, results in almost exclusive formation of a single (syn) diastereomer **220** (Scheme 80). This compound can be completely epimerized under basic conditions to afford the alternate (anti) diastereomer **221**. If more than one equivalent of sodium phenylthiolate is used in the coupling reaction the anti diastereomer is obtained exclusively. Likewise, coupling of the sodium enolate of dibenzylmalonate to **132** results in immediate formation of the two possible diastereomers with the syn compound predominating (Scheme 81). Extended reaction times result in epimerization and only the anti diastereomer is obtained. It is postulated that initial coupling takes place via S_N2 displacement of the bromide to give the syn diastereomer but epimerization occurs under the basic conditions involved to give only the anti compound. This hypothesis is further borne out by the fact that oxazinone **136** will undergo at least partial base catalyzed epimerization (the reaction could not be followed by TLC and was arbitrarily quenched after 30 min.), while oxazinone **143** will not (Equations 19 and 20). That only the anti compound is obtained upon treatment of the oxazinones **218** and **220** with base is presumably a reflection of the relative thermodynamic stabilities of the two diastereomers.

SCHEME 80

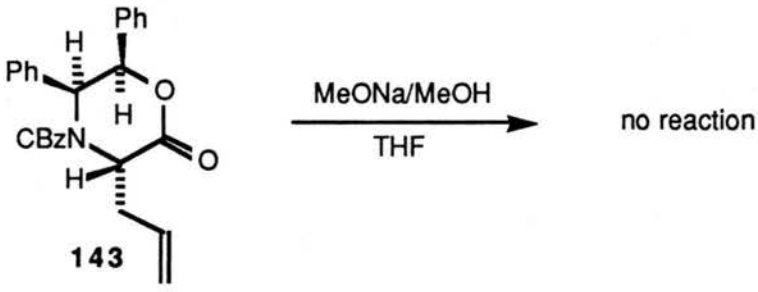


SCHEME 81





Equation 19



Equation 20

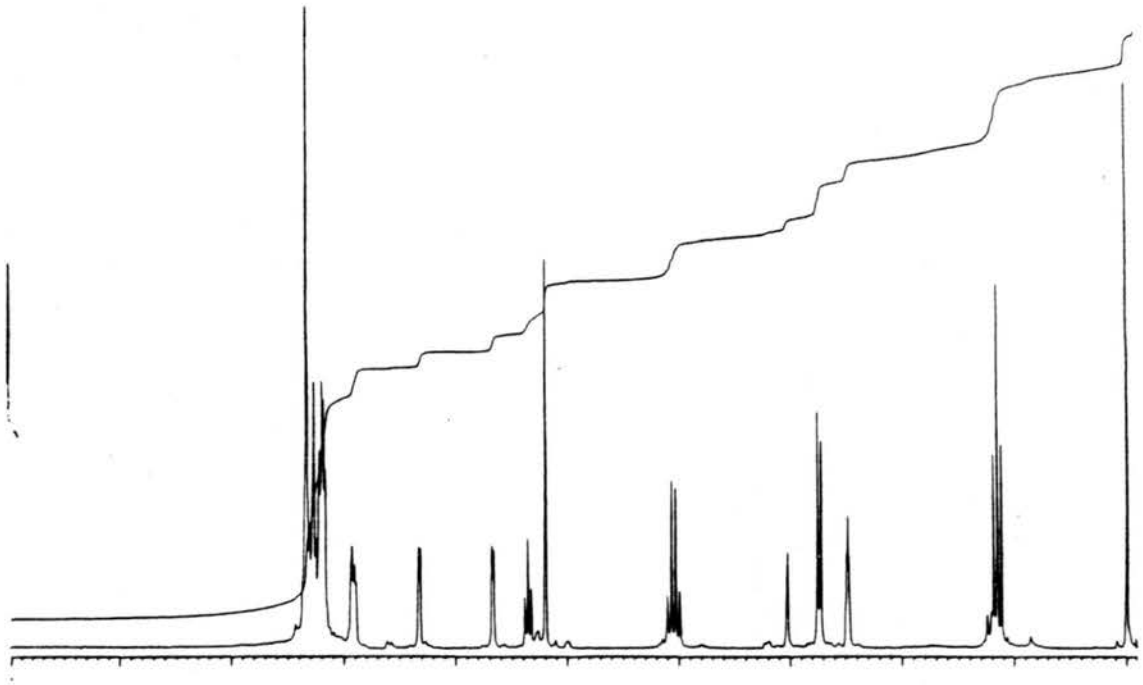
Organometallic reagents (alkyl zincs, alkyl cuprates) also couple with **132** to afford only the anti diastereomer. The mechanism of coupling for these reagents is not known but could involve nucleophilic displacement of the bromide or a radical (electron transfer) process. Because of the considerable amount of reduced oxazinone **108** formed, it is probable that the reaction proceeds by an electron transfer process. Any <u>syn</u> diastereomer that may be formed during this reaction will be epimerized to the <u>anti</u> diastereomer under the basic conditions employed.

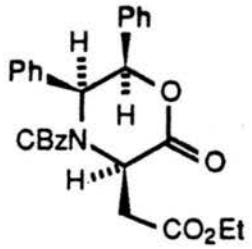
The foregoing discussion presents an admittedly simplistic model of the coupling mechanisms involved in homologation of bromoglycinate **132**, and does not take into account many factors. Nonetheless, the description adequately accounts for the observed experimental results and allows one, based on some estimate of the nucleophilicity of the reagent involved, to rationally modify the coupling conditions to increase observed diastereoselectivity. Thus, conditions that favor the S_N1 pathway (polar solvents, strong Lewis acids) will increase the amount of the anti diastereomer formed while conditions that

favor S_N2 coupling (non-polar solvents, weak Lewis acids) will lead to increased syn diastereomer formation.

As an addendum to the preceeding mechanistic discussion the determination of the absolute stereochemistry of the synthetic amino acids needs to be addressed. The stereochemistry of known amino acids prepared by this methodology can be established by comparison of the optical rotation of the synthetic amino acid to literature values. However, preparation of new and unnatural compounds necessitates determination of the absolute configuration at the stereogenic centers by other means. It would be advantageous to be able to carry out the stereochemical analysis at the oxazinone stage. With this goal in mind a number of ^1H NMR studies were undertaken in the hopes of developing a diagnostic tool. As has been mentioned several times previously the spectra of the N-protected 1,4-oxazine-2-ones are characterized by broad, ill-defined absorptions. Fortunately, ^1H NMR analysis can be carried out at elevated temperatures (120°C, DMSO-d_6) allowing one to obtain well resolved spectra (Figure 10).

Comparison of the syn and anti diastereomers, in the conformations that have been assumed to predominate, shows that for the syn diastereomer methine proton H_a is proximal to protons H_b and H_c while for the anti diastereomer proton H_a is considerably removed (Figures 11 and 12). It is believed that this sytem should lend itself nicely to stereochemical determination by Nuclear Overhauser Enhancement (NOE) studies. Irradiation of the resonance for H_a should result in some enhancement of H_b and/or H_c in the syn compound, but no effect should be observed for the anti compound. The several high temperature NOE experiments thus far carried out have given some interesting, albeit inconclusive, results. A Nuclear Overhauser Enhancement study was carried out on oxazinone **136** (Figure 11, R = CH_2CO_2Et). Irradiation at the H_a resonance (δ 5.35) afforded a difference spectrum (the spectrum obtained upon Fourier transformation of the FID resulting from subtraction of a control FID from that of the sample irradiated at the resonance of interest) that showed a positive enhancement of the resonance at δ6.32 and an





136

Figure 10 ^{1}H NMR spectra of **136** .
Top spectrum : (200 MHz) obtained in DMSO-d_6 at 120°c.
Bottom spectrum: (270 MHz) obtained in $CDCl_3$ at 25°c.

unexpected negative enhancement of the absorption at δ 5.68 (Figure 13). At first, the negative enhancement was thought to be due to power overflow (a partial decoupling). However, the very low power used during the double irradiation experiment and the considerable chemical shift differences of the resonances makes this explanation seem unlikely.

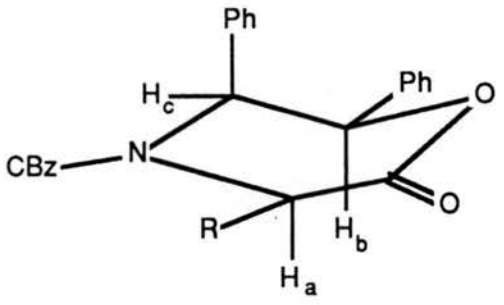


Figure 11

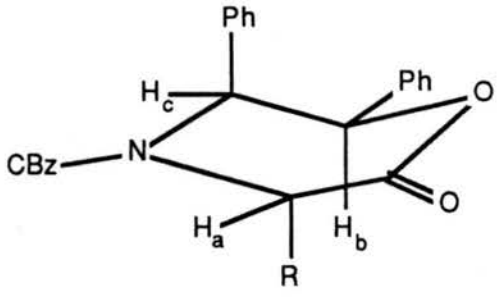


Figure 12

According to Noggle and Schirmer,[77] a three spin system having a geometry such that $r_{13} >> r_{12} \sim r_{23}$ (Diagram 1) and the 1-2-3 angle is obtuse (more accurately, $\rho_{13} << \rho_{12} \sim \rho_{23}$ where ρ_{12} = dipole-dipole relaxation between spins 1 and 2 and is inversely porportional to r^6) will show a positive enhancement for spin 2 and a negative enhancement for spin 3 upon irradiation of spin 1. Irradiation of spin 2 will show (smaller) positive enhancements at spins 1 and 3, while irradiation of spin 3 will give a positive enhancement at spin 2 and a negative enhancement at spin 1.

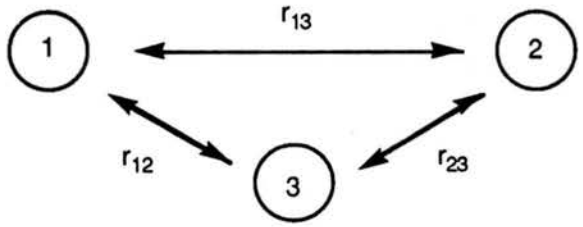


diagram 1

If the linear 3 spin case applies to the oxazinone, then irradiation of spin 2 (the δ 6.32 resonance) should result in a positive enhancement for spins 1 and 3. This has been observed but the enhancements are small (Figure 14). Also, any enhancement observed at δ 5.63 may be due to a partial (scalar) decoupling.

As expected, NOE experiments carried out on two of the anti diastereomers (Figures 15 and 16, R = CH_3, C_2H_5) show no enhancements at all. Finally, an NOE analysis of oxazinone **186** (formed by condensation of a silyl ketene acetal with **132** and therefore expected to afford the syn diastereomer) gave a difference spectrum analogous to **136**; there was a positive enhancement at the downfield benzylic methine resonance and a negative enhancement at the upfield benzylic methine resonance (Figure 17). While not conclusive, these results indicate that a relatively simple diagnostic tool for determination of the stereochemistry of the oxazinones may be developed using ^1H NMR spectroscopy.

A simpler indication of the stereochemistry of the oxazinones can be based on the observed chemical shift differences of the resonances for protons H_b and H_c. Thus, for the anti diastereomers of the coupled oxazinones, the difference in chemical shift (Δδ) for H_b and H_c ranges from 0.94-1.13 ppm while Δδ for the syn diastereomers ranges from 0.60-0.68 ppm (see Figure 18). In addition, all of the homologated heterocycles thus far prepared that possess the anti stereochemistry have been crystalline compounds while the syn diastereomers have been oils. No explanations for these phenomena are offered, but they are nonetheless real, and can serve as a reasonable indications of the oxazinone stereochemistry.

The procurement of chiral, non-racemic α-monosubstituted α-amino acids is of considerable importance in the fields of organic chemistry, biochemistry, and medicinal chemistry. While there has been vigorous research carried out in the area of enantioselective amino acid synthesis with some notable success, there remains a need for general routes to these compounds.

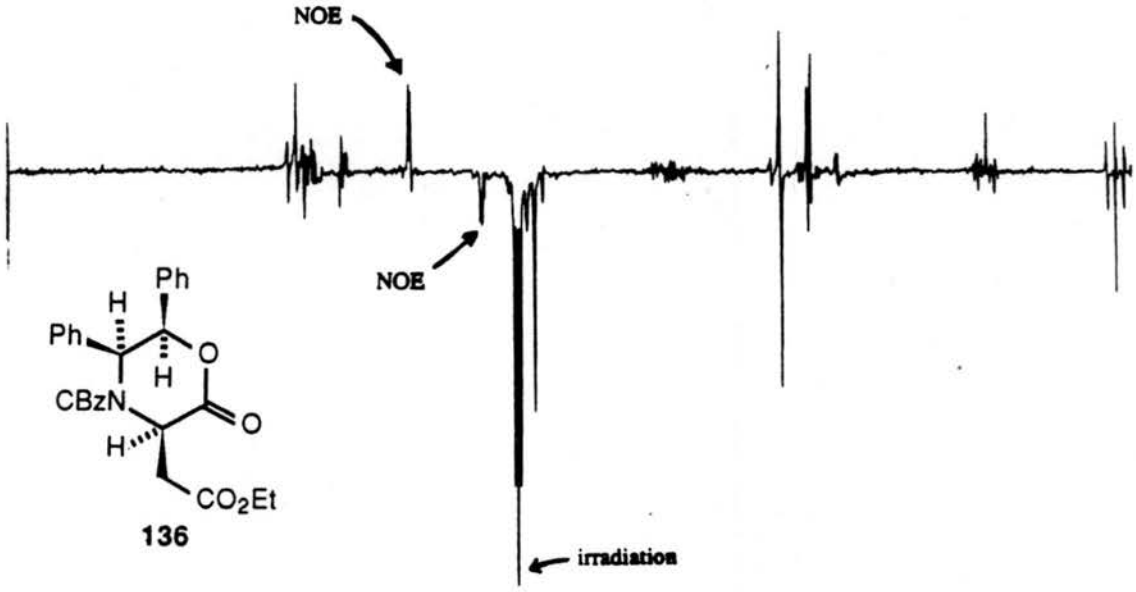


Figure 13 ^{1}H NMR NOE difference spectrum obtained upon irradiation of **136** at the δ 5.35 resonance.[(200 MHz)(DMSO-d_6)(393°K)]

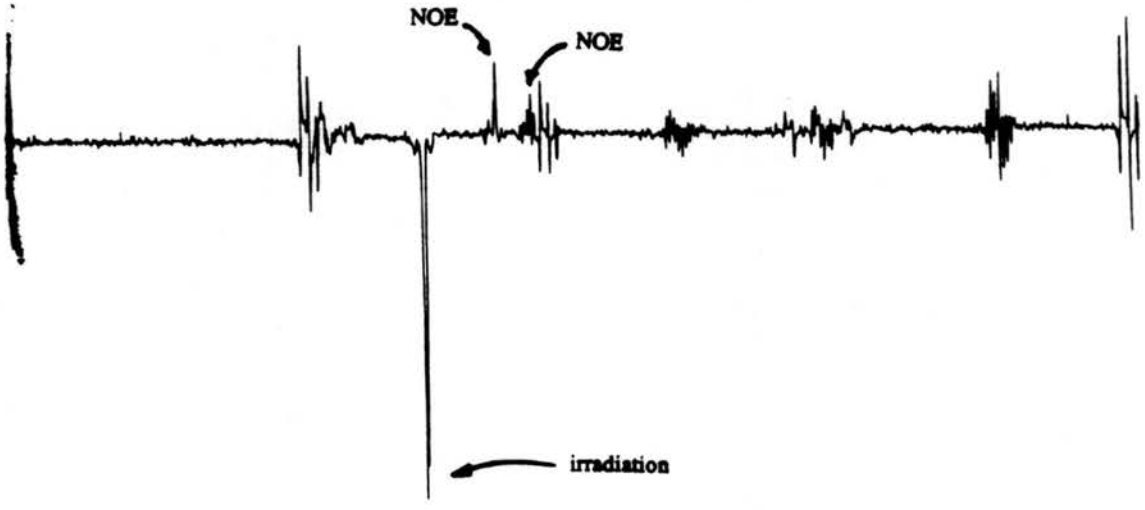
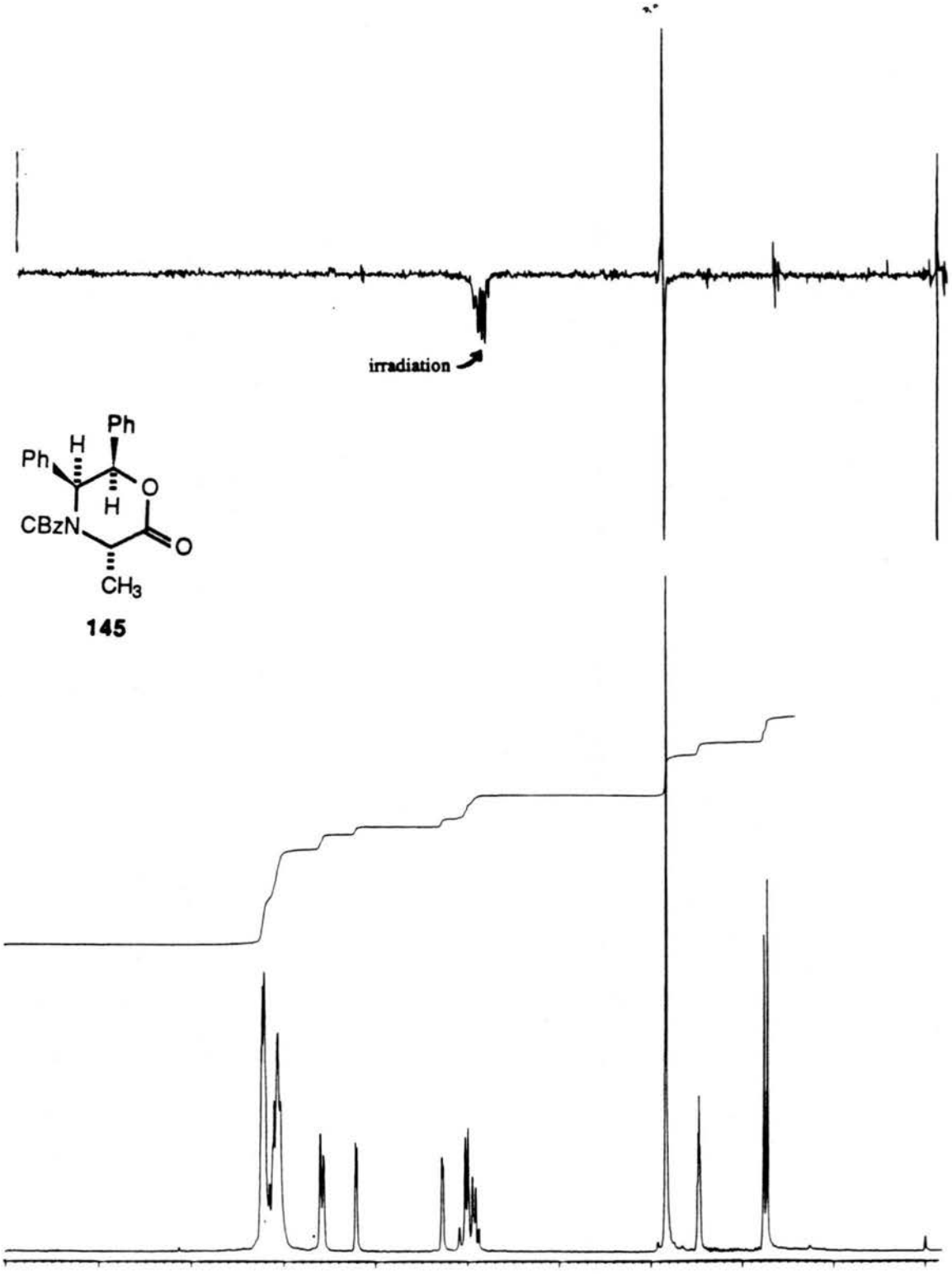
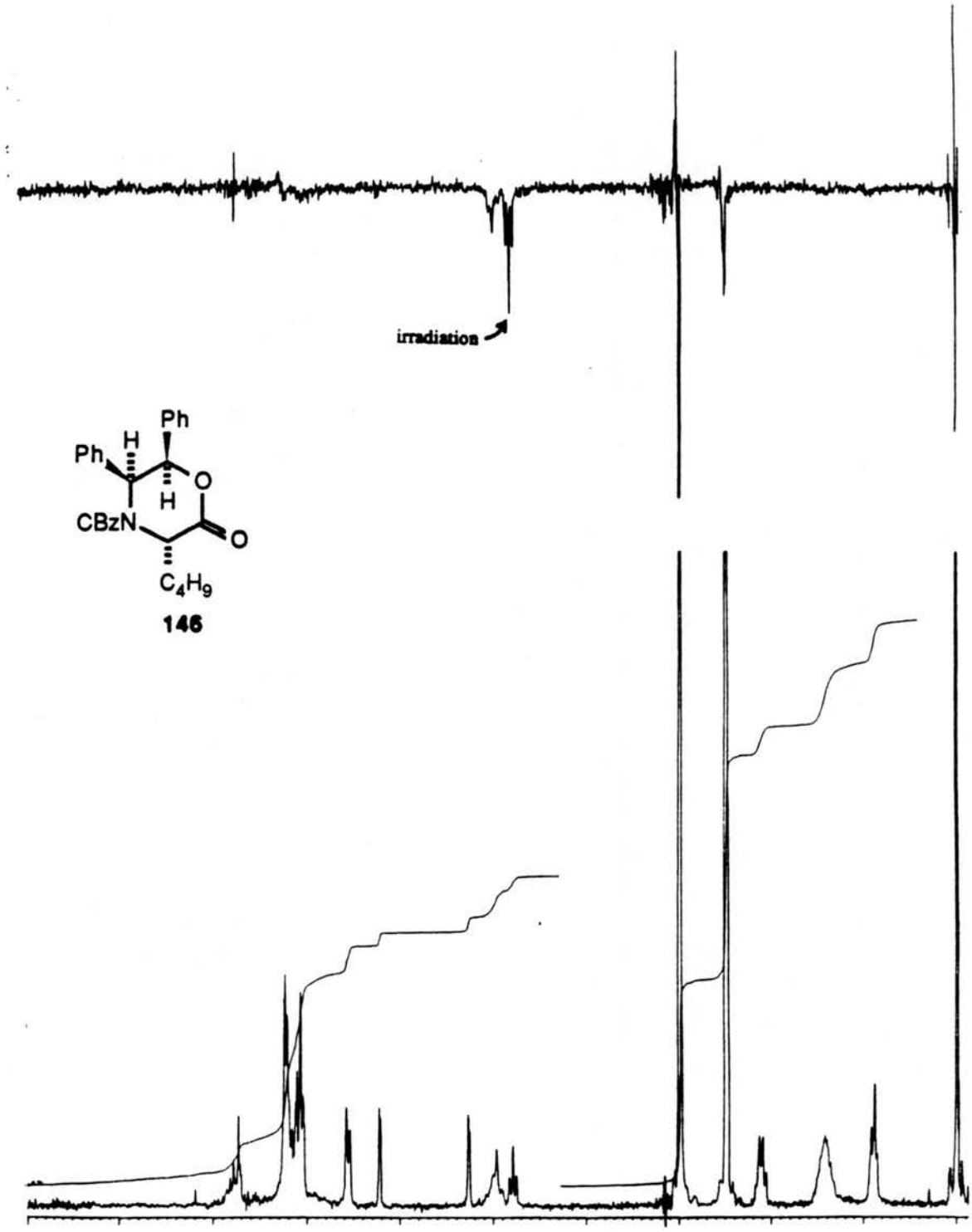


Figure 14 ^{1}H NMR NOE difference spectrum obtained upon irradiation of **136** at the δ6.32 resonance. [(200 MHz)(DMSO-d_6)(393°K)]



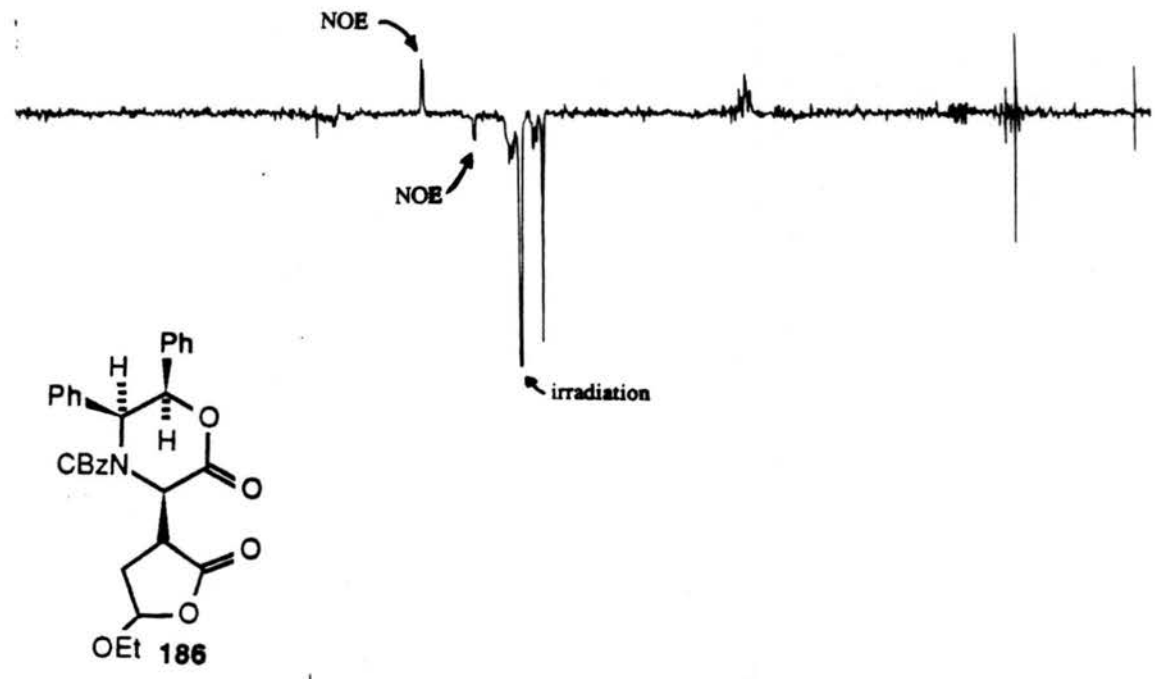
145

Figure 15 Bottom: ^{1}H NMR (200 MHz) spectrum of **145** in DMSO-d_6 at 393°K.
Top: ^{1}H NMR NOE difference spectrum obtained upon irradiation of **145** at the δ 4.92 resonance. [(200 MHz)(DMSO-d_6)(393°K)]



146

figure 16 Bottom: ^{1}H NMR (200 MHz) of **146** in DMSO-d_6 at 393°K.
Top: ^{1}H NMR NOE difference spectrum obtained upon irradiation of **146** at the δ 4.80 resonance. [(200MHz)(DMSO-d_6)(393°K)]



186

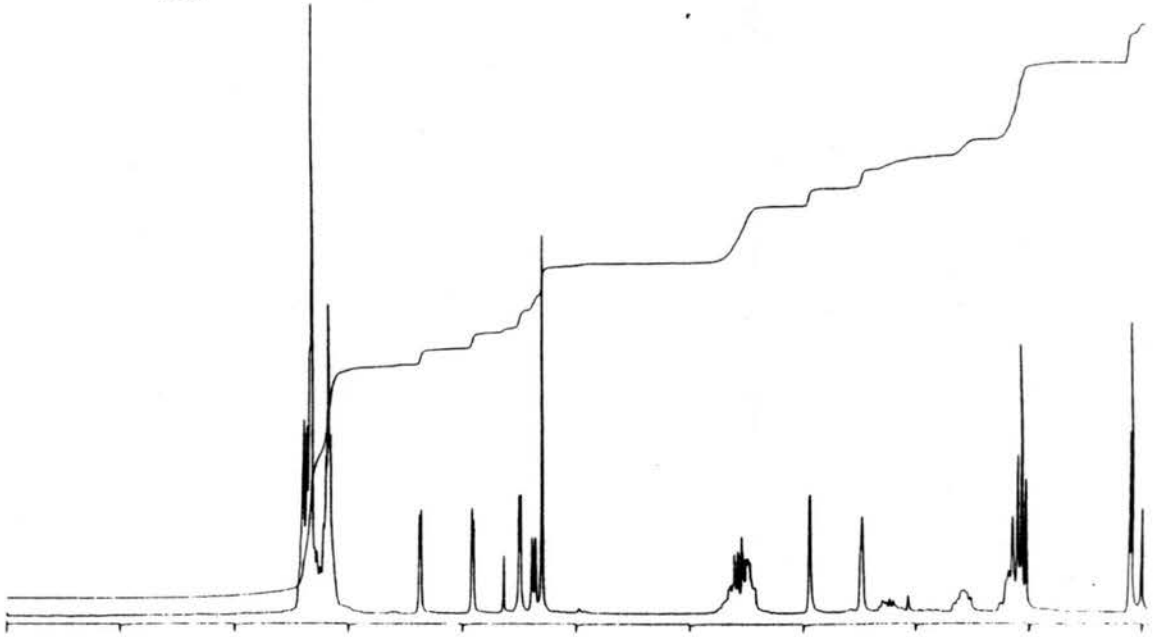


Figure 17 Bottom: ^{1}H NMR (200 MHz) of **186** in DMSO-d_6 at 393°K.
Top: ^{1}H NMR NOE difference spectrum obtained upon irradiation of **186** at the δ 5.49 resonance. [(200 MHz)(DMSO-d_6)(393°K)]

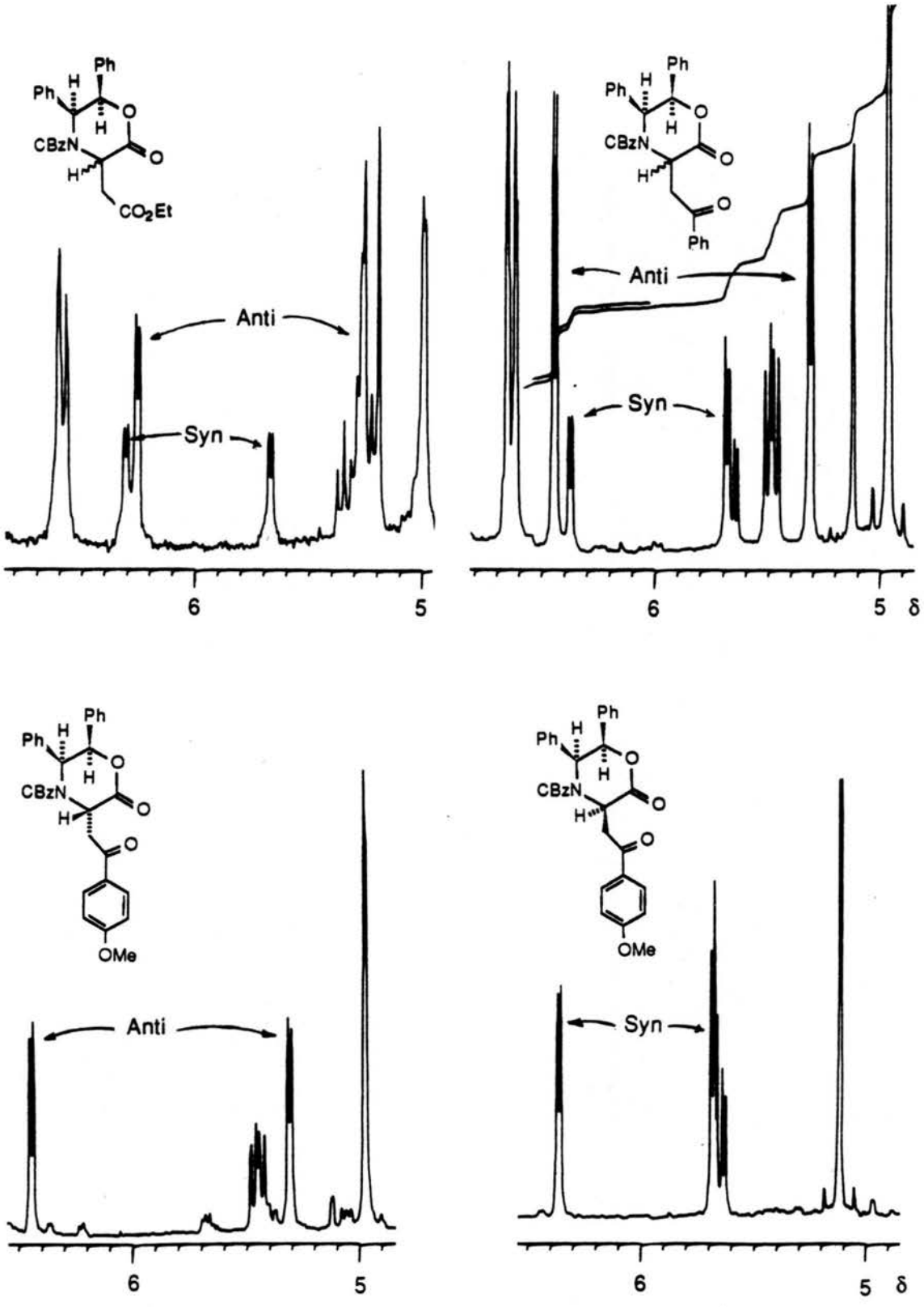


Figure 18 Relative $\Delta\delta$ of H_b and H_c for representataive oxazinones. Spectra obtained at 393°K in DMSO-d_6

An enantioselective amino acid synthesis has been developed based on electrophilic glycinate **132**, readily obtained from template **108**. Oxazinone **108**, in turn, can be prepared on a large scale from inexpensive starting materials. Bromoglycinate **132** couples with a variety of reagents to afford the homologated oxazinone in moderate to good yield. For most of the coupling reactions good diastereoselectivity is achieved under the standard coupling conditions (THF, $ZnCl_2$) or, when necessary, by appropriate modifications thereof. The hydrogenolysis/deprotection of the heterocycle is remarkably clean and facile, affording the desired amino acid with minimal manipulation. Use of a dissolving metal reduction/deprotection allows the synthesis of unsaturated amino acids, and utilization of the t-BOC protected oxazinone **156** permits the direct synthesis of BOC protected amino acids. While the full scope and limitations of our procedure have yet to be established, it is believed this route nicely complements the existing chiral glycine enolate methodology and offers considerable potential for the synthesis of rare and unnatural α-amino acids.

CHAPTER IV

EXPERIMENTAL SECTION

A. General Information

Melting points were determined in open-ended capillary tubes on a "Mel-Temp" apparatus, and are uncorrected. Infrared spectra were recorded on a Beckman model 4240 spectrophotometer and were obtained on NaCl pellets. Absorptions are reported in cm^{-1}. ^{1}H NMR spectra were recorded on the following instruments: Varian T-60 spectrometer without lock, Brucker WP-200SY 200 MHz spectrometer with lock, or Brucker WP-270SY 270 MHz spectrometer with lock. The field strength (MHz) is indicated for each spectrum in the experimental section. ^{19}F NMR spectra were obtained on the Brucker WP-200SY 200 MHz spectrometer with lock. Chemical shifts are reported in parts per million downfield from the internal standard, which is specifically indicated for each compound in the experimental section as δ - standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublets, the terms J_{vic} and J_{gem} refer to the vicinal or geminal proton coupling constants.

Low resolution mass spectra were obtained on a V. G. Micromass Ltd., Model 16F spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, and by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

Optical rotations were obtained on a Perkin-Elmer 24 polarimeter at wavelength 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of one ml. Specific rotations, $[\alpha]_D$, were reported in degrees per decimeter at the specified temperature and the concentration (c) given in grams per 100 ml in the specified solvent.

The single crystal X-ray analysis was obtained on a Nicolet R3m/E diffractometer.

B. Chromatography

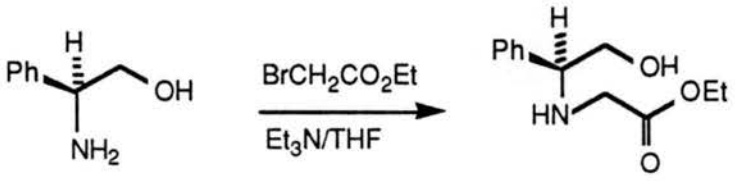
Analytical thin layer chromatography was performed on E. Merck 0.25 mm or 0.50 mm silica gel 60 F-254 layers backed by glass. Visualization on TLC was achieved with ultraviolet light, I_2 developing chamber and/or heating of TLC plates submerged in a 5% (by weight) solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column and flash chromatography were performed using Silica Woelm (32-63 μm) silica gel, in which the mixtures were preadsorbed on the silica gel. Radial chromatography was done on 1-4 mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron model 7924.

C. Reagents and Solvents

Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Diisopropyl amine was distilled from CaH_2 and kept under N_2 over activated 4A molecular sieves. n-Butyllithium was obtained from Ventron and was titrated (diphenylacetic acid, -78°C, THF) prior to use. Lithium diisopropyl amide (LDA) was freshly prepared by dropwise addition of n-butyllithium in hexane to a stirred solution of diisopropylamide in THF at 0°C and was used after stirring 10 min. LDA solutions were transferred via cannula to the reaction vessel using N_2 pressure. Diethylether was freshly distilled from sodium benzophenone ketyl under N_2 atmosphere. Dry methylene chloride, chloroform, and carbon tetrachloride were obtained by distillation over P_2O_5. Trimethylsilyl chloride was distilled from CaH_2 and immediately used. When required, dry DMF, DMSO, pyridine, 2,6-lutidine, HMPA, oxalyl chloride, acetonitrile, trifluoroacetic anhydride were taken via dry syringe from storage over activated 3A or 4A sieves after distillation from an appropriate reagent. All organic intermediates were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.

D. General Experimental Considerations

All moisture or oxygen sensitive reactions were conducted in glassware that was flame dried under high vacuum (0.5-2.0 mm Hg) and then purged with N_2. All reactions were magnetically stirred with Teflon coated stir bars. The following low temperature baths were used: 0°C (Ice water), -78°C (acetone, dry ice), -105°C to -100°C (4% water in methanol, liquid nitrogen). The term concentrated refers to solvent removal under the vacuum achieved by a water aspirator attached to a Buchi rotary-evaporator. Residual solvent was removed at reduced pressure (0.5-0.5 mm Hg) using a vacuum pump.

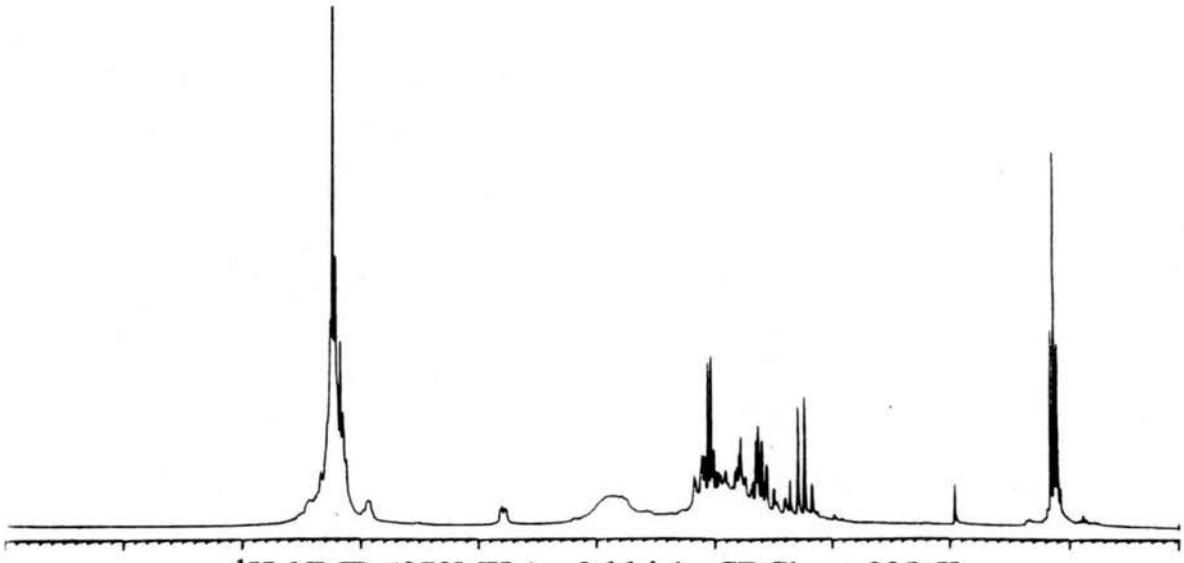


109 **114**

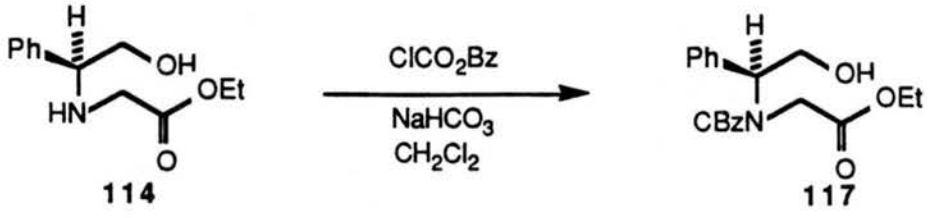
(1'S)-Ethyl-N-(2'-hydroxy-1'-phenyl)glycinate (114)

To a stirred solution of phenylglycinol (3 g, 21.97 mmol, 1 equiv) in THF (50 mL) at 0°C was added ethylbromoacetate (2.4 mL, 21.9 mmol, 1 equiv) followed by addition of triethylamine (6.1 mL, 43.7 mmol, 2 equiv). The mixture was stirred overnight and the white triethylamine hydrochloride salt precipitate was filtered. The filtrate was concentrated in vacuo, diluted with CH_2Cl_2 and washed with water. The aqueous layer was back extracted 3x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to yield 5.3 g **114** as an oil which was used crude.

IR(NaCl, neat): 3500-3200, 3050, 2980, 1745, 1655, 1445, 1415 cm^{-1}.



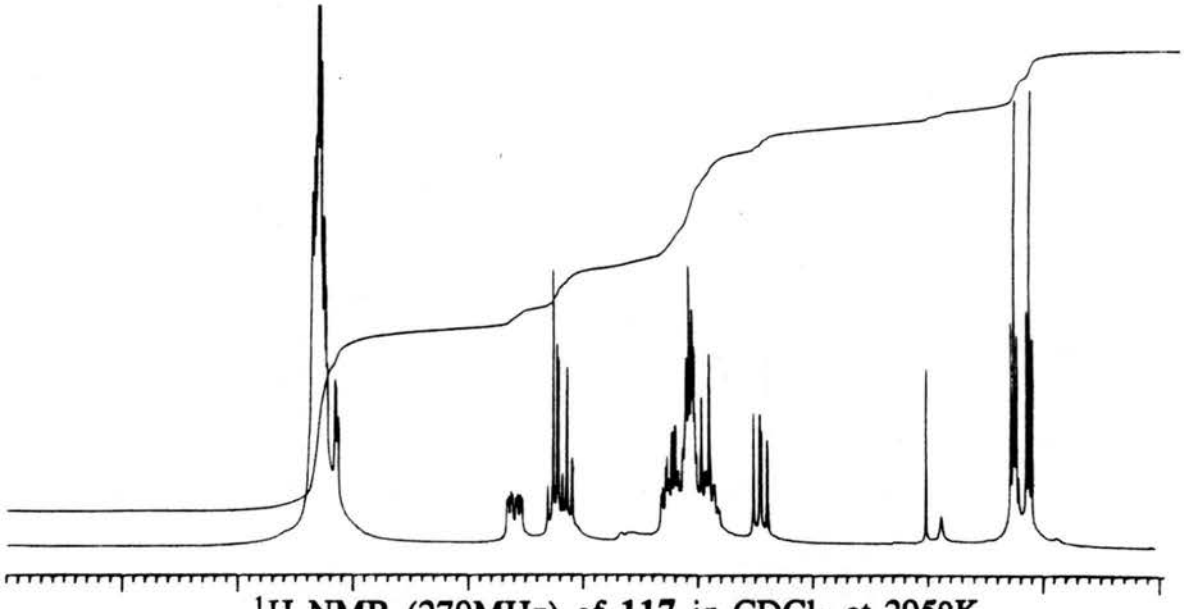
^{1}H NMR (270MHz) of **114** in $CDCl_3$ at 295°K.



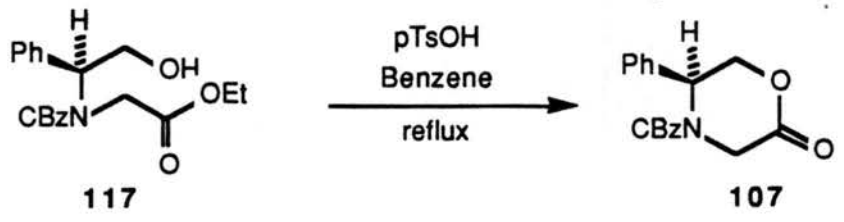
(1'S)-Ethyl-N-benzyloxycarbonyl-N-(2'-hydroxy-1'-phenyl)glycinate (117)

To a stirred solution of **114** (8.13 g, 36.45 mmol, 1 equiv) in CH_2Cl_2 (150 mL) was added saturated aqueous $NaHCO_3$(150 mL). To this rapidly stirred mixture was added benzylchloroformate (5.5 mL, 38.27 mmol, 1.05 equiv). After 2 h the aqueous layer was separated and thoroughly extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and separated by flash column chromatography on silica gel (eluted with 2:3 EtOAc/hexanes) to afford 8 g (61%) **117** as an oil.

IR (NaCl, neat): 3460, 3060, 3030, 2980, 1730, 1700, 1455, 1405, 1330 cm^{-1}.



^{1}H NMR (270MHz) of **117** in $CDCl_3$ at 295°K.

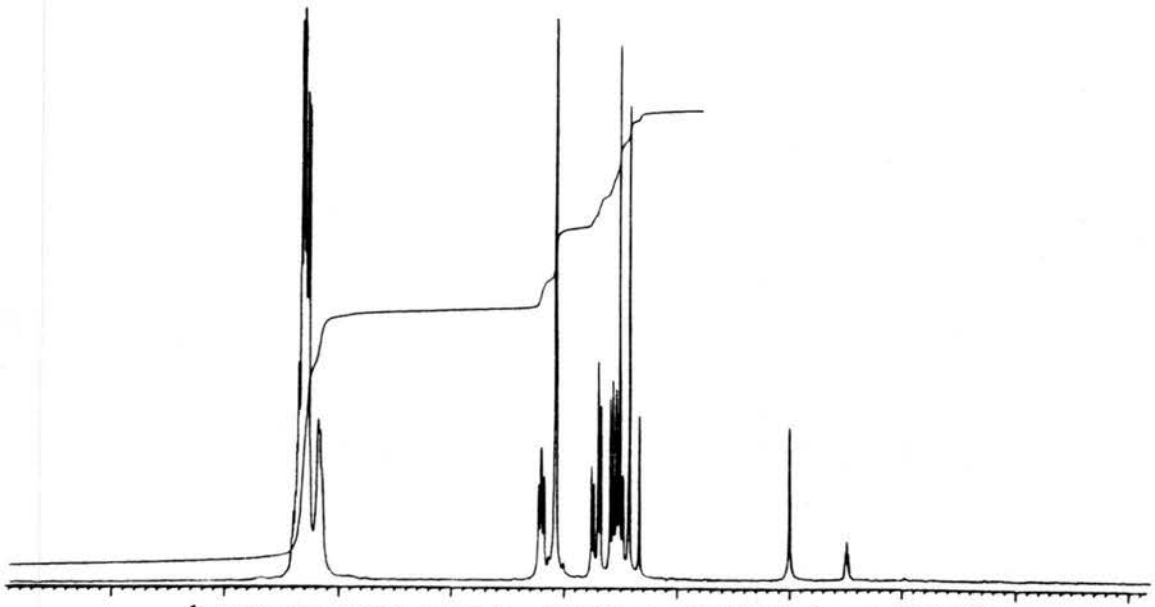


117 **107**

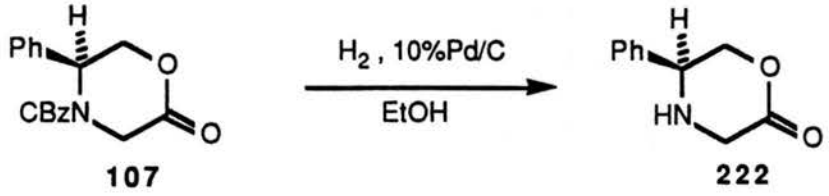
(5S)-4-Benzyloxycarbonyl-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (107)

A stirred solution of **117** (2.7 g, 7.60 mmol, 1 equiv) in benzene (30 mL) in a 50 mL flask equipped with a Dean-Stark trap was heated and maintained at reflux until 20 mL benzene had been collected. The mixture was cooled, concentrated and recrystallized (EtOAc/hexanes) to afford 2.1 g (90%) **107** as off-white crystals.

^{1}H NMR (200 mHz)(383°C)(DMSO-d_6): 4.37(1H, 1/2ABq, J=17.3Hz); 4.55(1H, 1/2ABq, J=17.3Hz); 5.51(1H, dd, J_{gem}=5.11Hz); 4.71(1H, dd, J_{gem}=12.0Hz, J_{vic}=4.2Hz); 5.07(2H, s); 5.20(1H, dd, J_{vic}=4.2Hz, J_{vic}=5.1Hz); 7.1-7.35(10H, m). IR(NaCl, CH_2Cl_2): 3050, 2980, 2920, 1765, 1705, 1410, 1205 cm^{-1}. Analysis (recrystallized from EtOAc/hexanes) calculated for $C_{18}H_{17}NO_4$: C, 69.44, H, 5.50, N, 4.49. Found: C, 69.46, H, 5.52, N. 4.50. $[\alpha]_D^{25}$ = -58.1 (c = 1, CH_2Cl_2), mp 122.4-123.4°C.



^{1}H NMR (200 MHz) of **107** in DMSO-d_6 at 393°K.

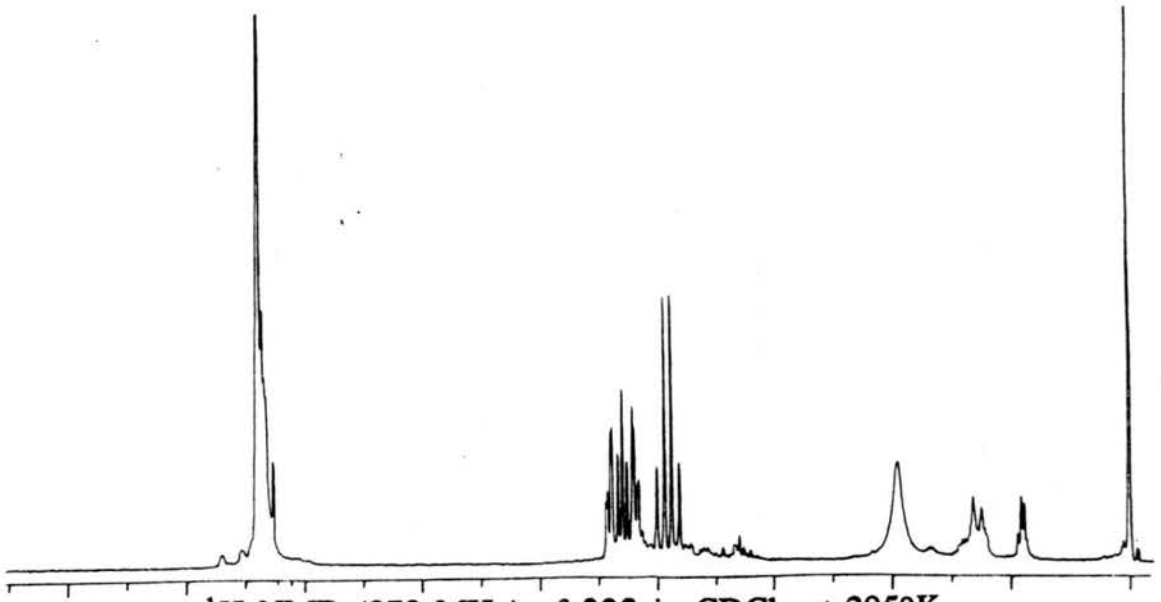


107 **222**

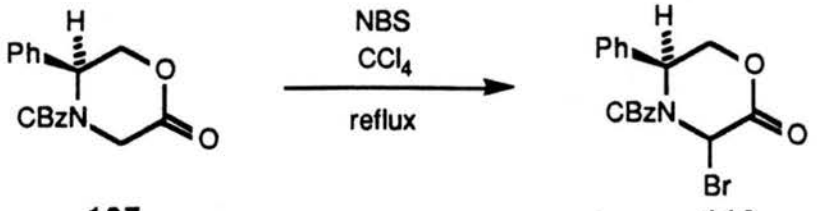
(5S)-5-Phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (222)

A stirred solution of **107** (50 mg, 0.160 mmol, 1 equiv) in absolute ethanol (10 mL) was degassed under N_2. 10% Pd on carbon (51 mg, 0.016 mmol, 0.1 equiv) was added and H_2 was bubbled through the mixture. After 5 minutes TLC analysis indicated complete conversion of the starting material. The flask was purged with N_2. The catalyst was filtered and the filtrate was concentrated and separated by PTLC silica gel (eluted with 2:3 EtOAc/hexanes) to afford 25.5 mg (89%) **222** as a clear oil.

^{1}H NMR (270 MHz)($CDCl_3$) δ $(CH_3)_4Si$: 1.95(1H, broad s); 3.88(2H, ABq, J=17.8Hz); 4.17(1H, dd, J_{vic}=2.9Hz, J_{gem}=10.1Hz); 4.30(1H, dd, J_{vic}=J_{gem}=10Hz); 4.41(1H, dd, J_{vic}=10Hz, J_{vic}=2.9Hz); 7.2-7.4(5H, m). IR(NaCl)($CDCl_3$): 3450, 3330, 2950, 2920, 1770-1720, 1500, 1455, 1405, 1310, 1300, 1240, 1205, 1095, 1025 cm^{-1}.



^{1}H NMR (270 MHz) of **222** in $CDCl_3$ at 295°K.

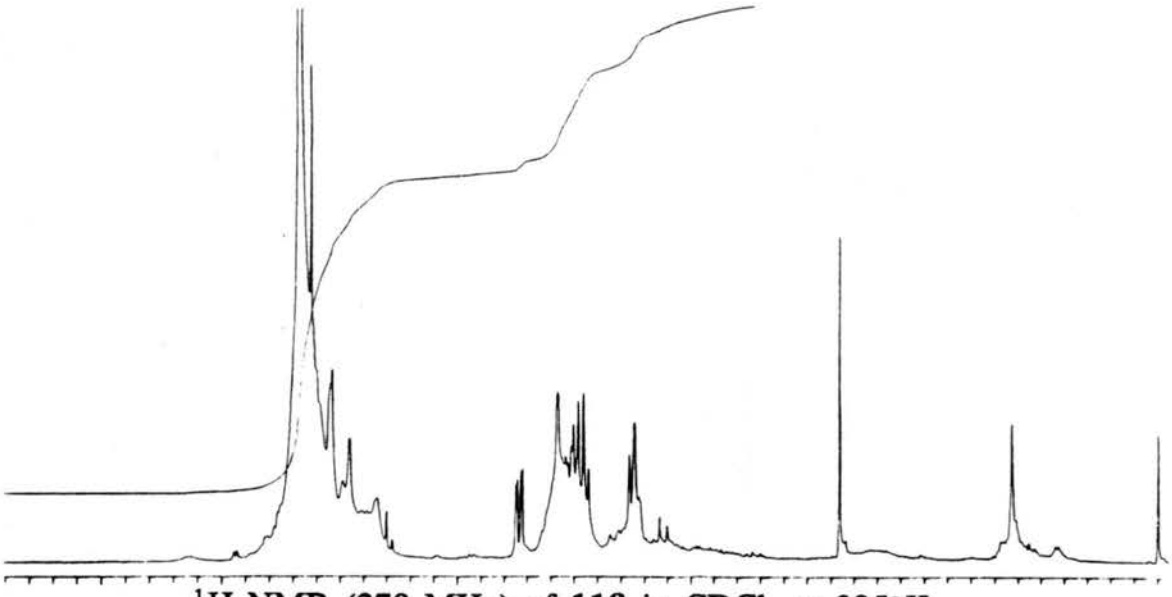


107 **118**

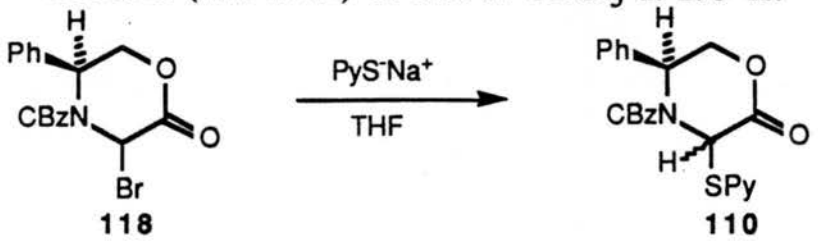
(5S)-4-Benzyloxycarbonyl-3-bromo-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (118)

To a dry flask containing **107** (80 g, 0.252 mmol, 1 equiv) was added distilled CCl_4 (25 ml). The mixture was brought to reflux. When all of **107** had dissolved, NBS (50.4 g, 0.282 mmol, 1 equiv) was added. The mixture was refluxed an additional 20 min. The flask was then cooled to 0°C, the succinimide filtered off and the solvent removed in vacuo leaving 105 mg (105%) crude **118** as a clear oil.

IR (NaCl)(CH_2Cl_2): 3050, 3030, 3920, 1770, 1720, 1490, 1450, 1395, 1280, 1260, 1218, 1150, 1124, 1060, 1047 cm^{-1}.



^{1}H NMR (270 MHz) of **118** in $CDCl_3$ at 295°K.

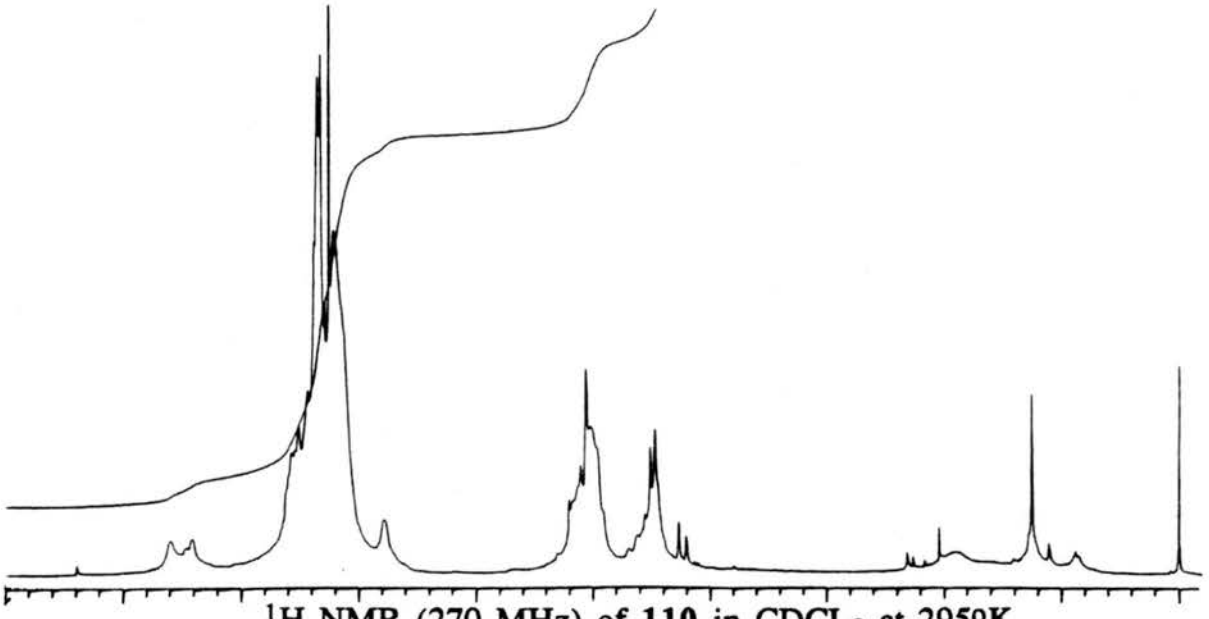


118 **110**

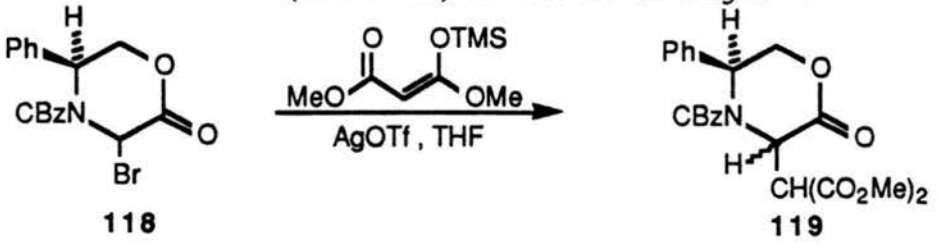
(5S)-4-Benzyloxycarbonyl-5-phenyl-3-(2'-pyridylthio)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (110)

To a suspension of NaH (10.6 mg, 0.440 mmol, 1.3 equiv) in dry THF (2 mL) was added 2-mercaptopyridine (45 mg, 0.406 mmol, 1.2 equiv). After 10 min. this mixture was transferred via syringe to a solution of **118** (132 mg, 0.34 mmol, 1 equiv) in dry THF (8 mL). After 30 min the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:3 EtOAc/hexanes) to afford a 94 mg (66%) **110**.

IR(NaCl, $CDCl_3$): 3060, 3030, 2950, 1760, 1705, 1570, 1450, 1395, 1340, 1275, 1250, 1200 cm^{-1}.



^{1}H NMR (270 MHz) of **110** in $CDCL_3$ at 295°K.

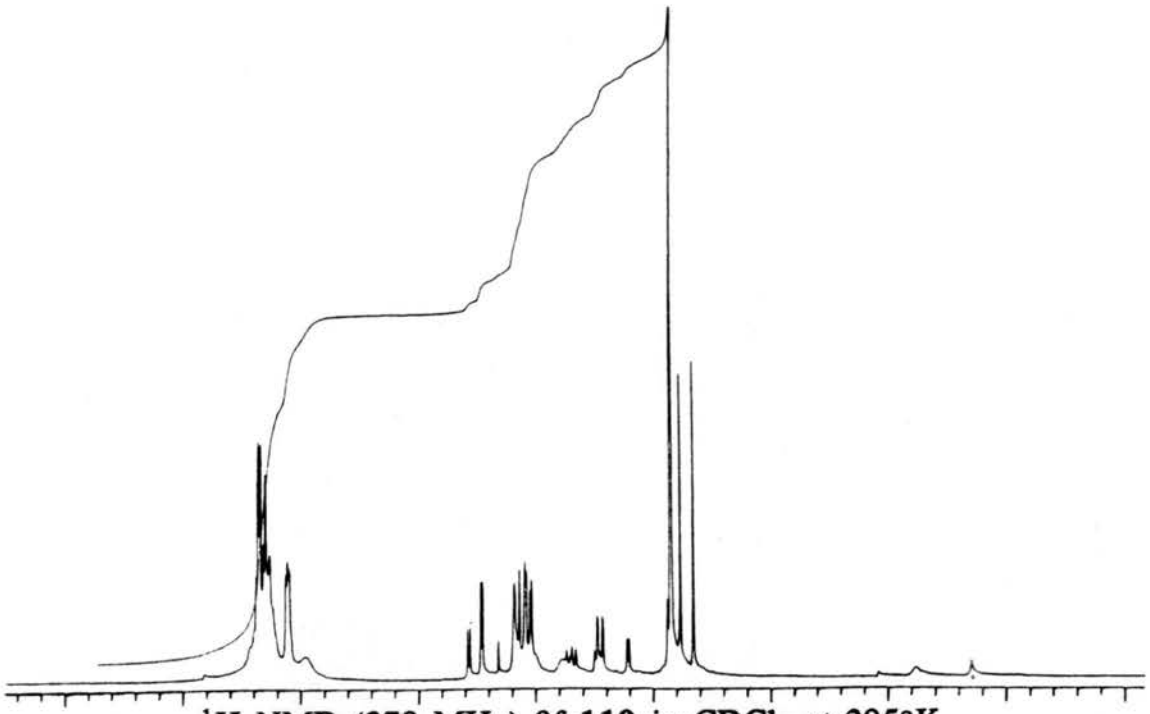


118 **119**

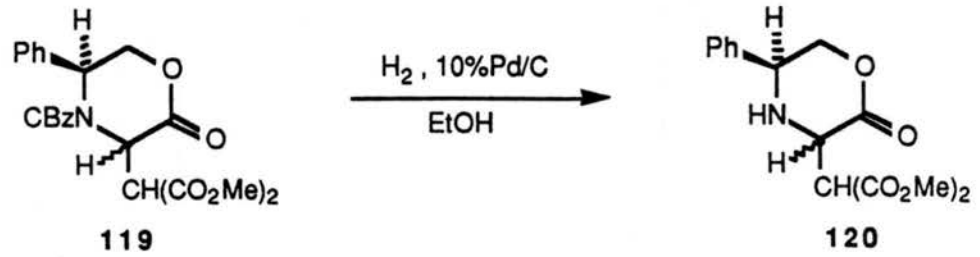
(5S)-4-Benzyloxycarbonyl-3-(2'-dimethylmalonyl)-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (119)

To a stirred solution of **118** (125.4 mg, 0.321 mmol, 1 equiv) in dry THF (7 mL) was added the silyl ketene acetal of dimethylmalonate (100 μL, 0.482, 1.5 equiv) followed by AgOTf (124 mg, 0.482 mmol, 1.5 equiv) resulting in the immediate formation of an off-white precipitate. The reaction mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic fractions were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:2 EtOAc/hexanes) to afford 120 mg (84%) **119** as a mixture of diastereomers.

IR(NaCl, neat): 3060, 3025, 2900, 1750, 1705, 1495, 1450, 1435, 1405, 1385 cm^{-1}.



^{1}H NMR (270 MHz) 0f **119** in $CDCl_3$ at 295°K.

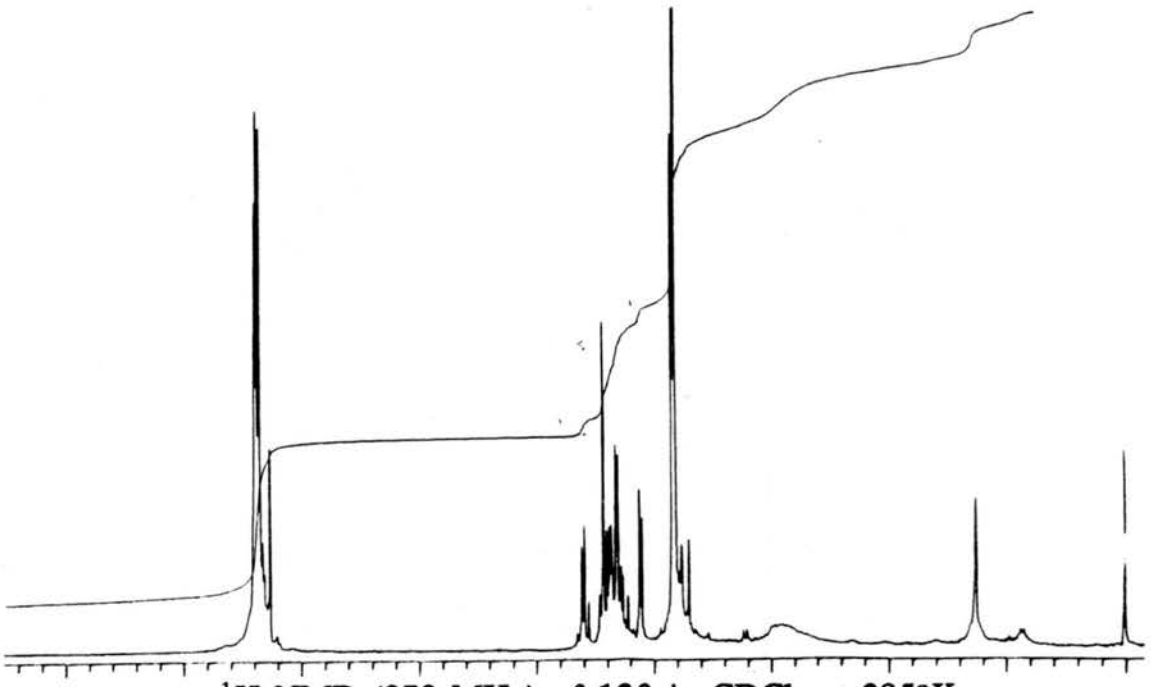


119 **120**

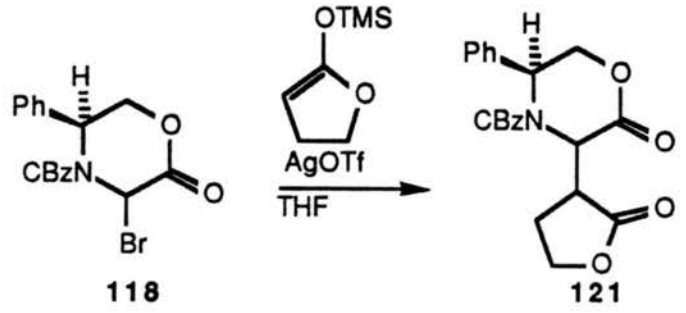
(5S)-3-(2'-Dimethylmalonyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (120)

To a stirred solution of **119** (53 mg, 0.142 mmol, 1 equiv) in 1:1 EtOH/THF (6 mL) was added 10% Pd on carbon (15.2 mg, 0.014 mmol, 0.1 equiv). Hydrogen was bubbled through the stirred mixture. After 1 h, the flask was purged with N_2, the catalyst was filtered off and the filtrate concentrated to afford 33 mg (75%) **120** as an approximately 2:1 mixture of diastereomers.

IR(NaCl, neat): 3340, 2955, 2750, 1735, 1440, 1285, 1200, 1105 cm^{-1}.



^{1}H NMR (270 MHz) of **120** in $CDCl_3$ at 295°K.



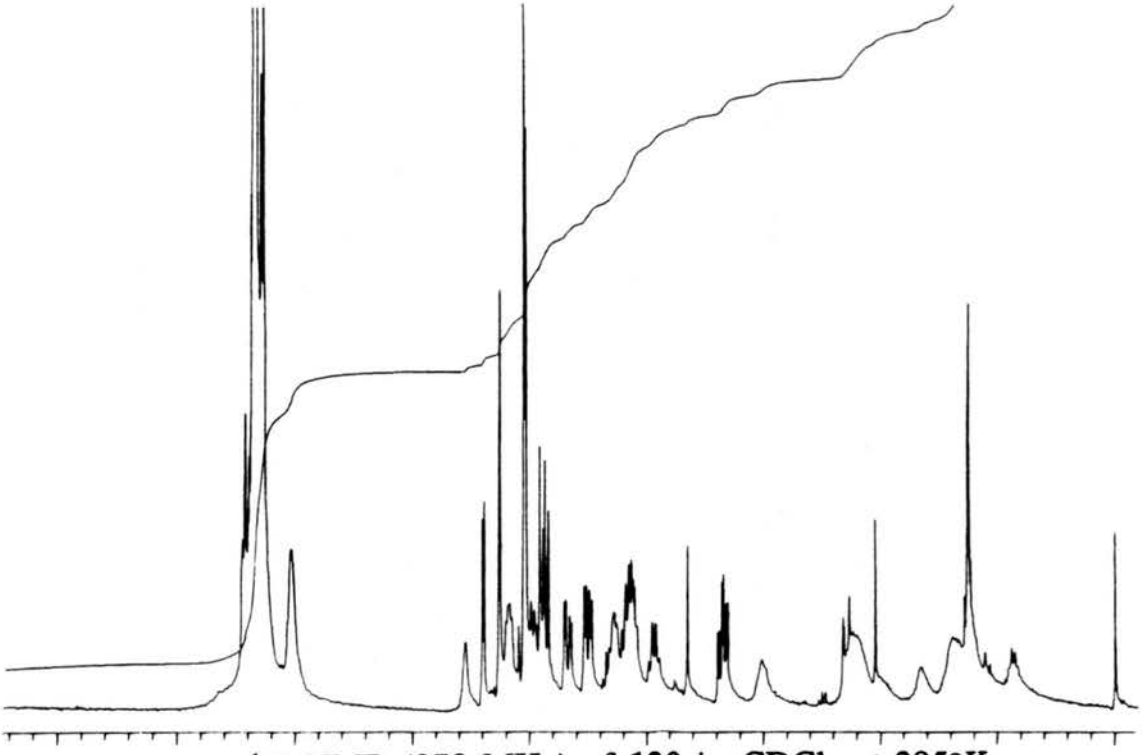
118 **121**

(5S)-4-Benzyloxycarbonyl-3(2'-γ-butyrolactonyl)-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (121)

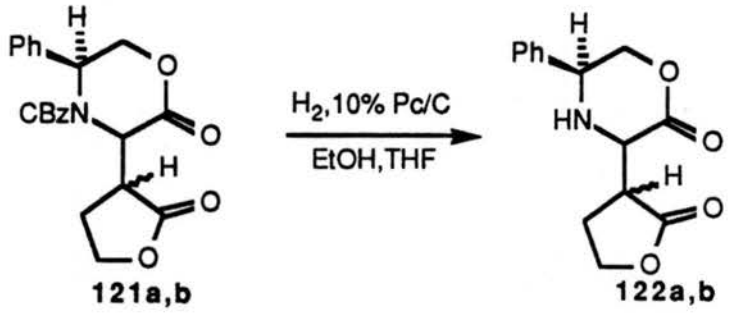
To a stirred solution of **118** (11.5 mg, 0.03 mmol, 1 equiv) in dry THF (0.5 mL) was added the silyl ketene acetal of γ-butyrolactone (7.8 μL, 0.045 mmol, 1.5 equiv) via syringe. AgOTf (11.4 mg, 0.0442 mmol, 1.5 equiv) was added resulting in the immediate formation of an off-white precipitate. TLC analysis indicated complete consumption of starting material. The mixture was diluted with CH_2Cl_2, poured into water and thoroughly extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium

sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 2:3 EtOAc/hexanes) to afford 7.8 mg (68%) **121** as an oil as a mixture of diastereomers.

IR(NaCl)(CH_2Cl_2): 3060, 3030, 2955, 2910, 1770, 1745, 1700, 1495, 1455, 1395, 1295, 1165, 1025 cm^{-1}. Mass spectrum m/e 304(M^+ - 91, 35%); 260 (104%).



^1H NMR (270 MHz) of **120** in $CDCl_3$ at 295°K.



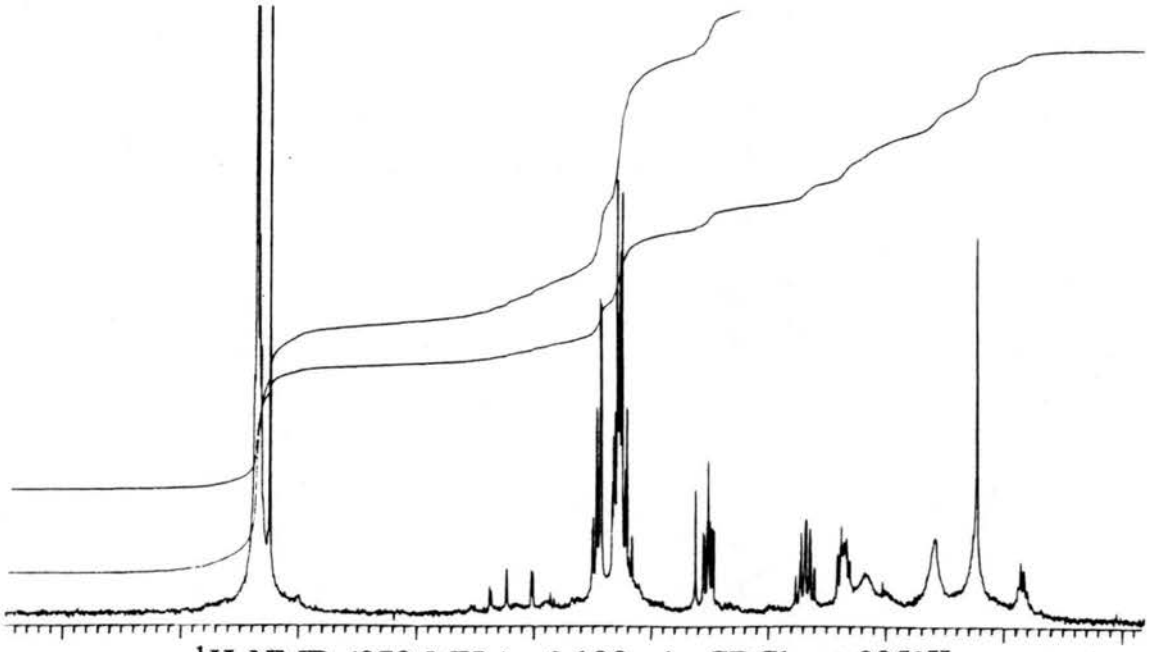
(5S)-3-(2'-γ-Butyrolactonyl)-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (122)

To a stirred solution of **121** (39.4 mg, 0.100 mmol, 1 equiv) in 1:1 THF/EtOH (5 mL) was added 10% Pd/C (10.6 mg 0.010 mmol, 0.1 equiv). Hydrogen was bubbled through the mixture for 20 min. The flask was purged with N_2. The catalyst was filtered.

The filtrate was concentrated, and separated by PTLC silica gel (eluted with 2:5 EtOAc/hexanes) to afford 8 mg (32.5%) **122**A as an oil and 7 mg (28.5%) **122**B as an oil.

122A

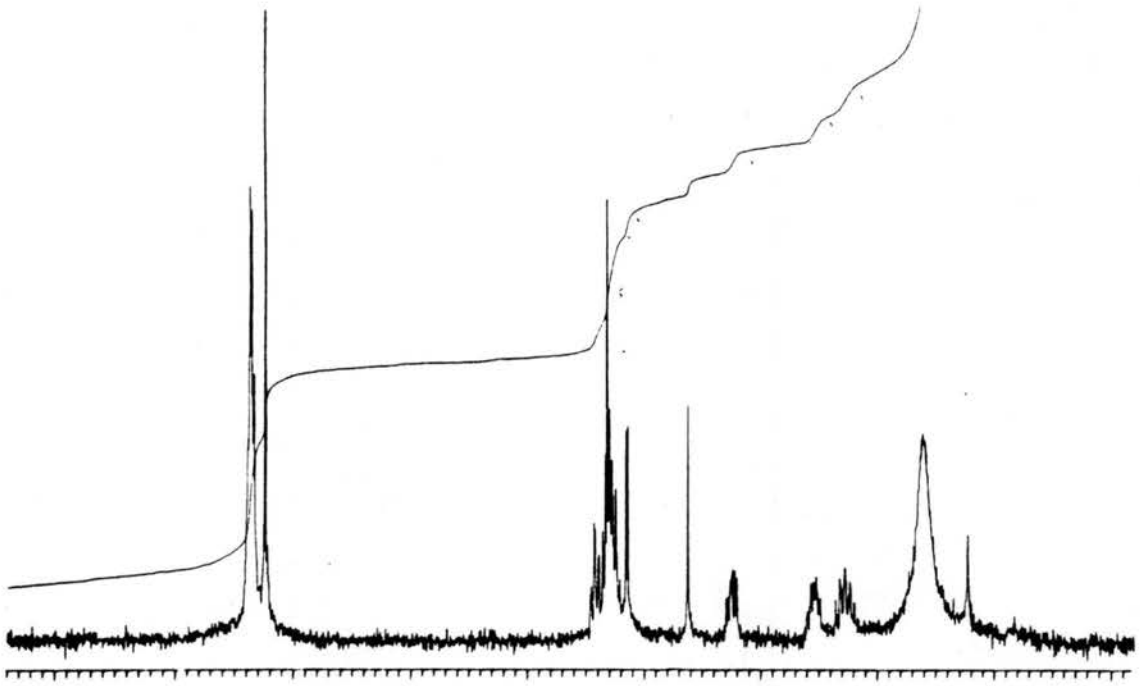
^{1}H NMR (270 MHz)($CDCl_3$) δ $(CH_3)_4Si$: 1.59(1H, s, broad); 2.38(1H, m); 2.68(1H, m); 3.62(1H, m); 4.1-4.3(4H, m); 4.44(1H, d, J=2.3Hz); 4.46(1H, m); 7.2-7.5(5H, m). IR(NaCl, neat): 3310, 2910, 1765, 1745, 1455, 1375 cm^{-1}. Mass spectrum m/e = 261(M^+, 22%), 260(23%), 259(65%).



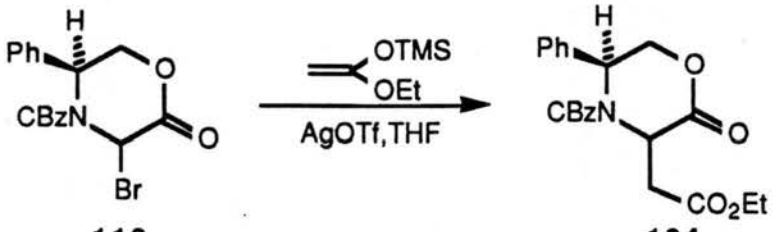
^{1}H NMR (270 MHz) of **122a** in $CDCl_3$ at 295°K.

122B

^{1}H NMR (270 MHz)($CDCl_3$) δ $(CH_3)_4Si$: 2.25(1H, m); 2.54(1H, m); 3.24(1H, m); 4.17(1H, d, J=4.5Hz); 4.25-4.45(5H, m); 7.2-7.4(5H, m). IR(KBr): 3325, 1760, 1450, 1375, 1320, 1205, 1124, 1015 cm^{-1}. Mass spectrum m/e 202(M^+ + 1, 7%). 261(M^+, 33%).



^{1}H NMR (270 MHz) of **122b** in $CDCl_3$ at 295°K.



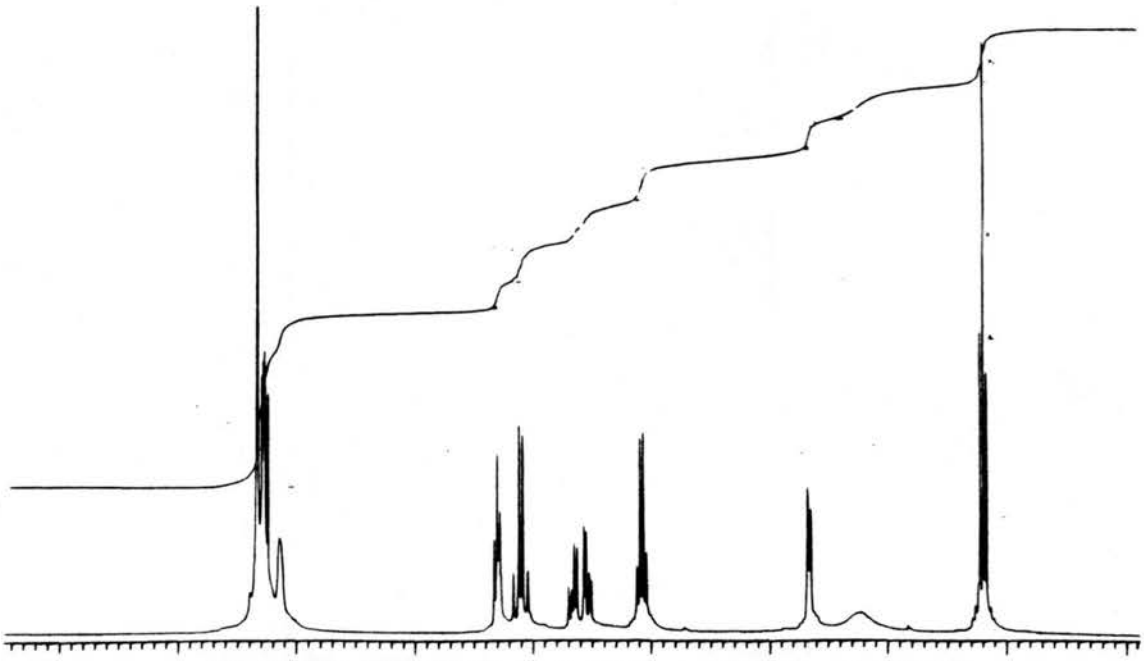
118 **124**

(5S)-4-Benzyloxycarbonyl-3-((ethoxycarbonyl)methyl)-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (124)

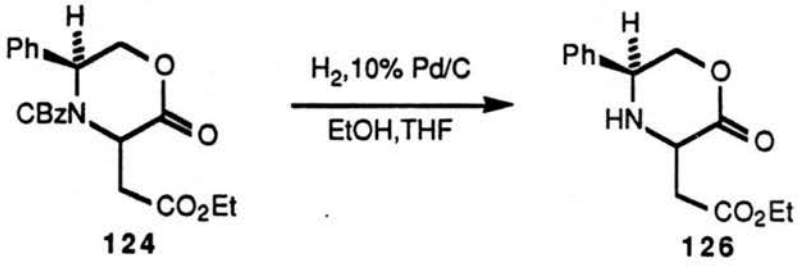
To a stirred solution of **118** (302 mg, 0.774 mmol, 1 equiv) in dry THF (10 mL) was added the t-butyldimethylsilyl ketene acetal of ethylacetate (364 μL, 1.935 mmol, 2.5 equiv) followed by addition of silver triflate (298 mg, 1.161 mmol, 1.5 equiv). After 15 min the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:3 EtOAc/hexanes) to yield 11.5 mg **124a** as an oil and 184.4 mg **124b** as an oil.

124B

^{1}H NMR (270 MHz)($CDCl_3$) δ $CHCl_3$: 1.2(3H, t, J=7Hz); 2.70(2H, d, broad); 4.08(2H, q, J=7Hz); 4.54(1H, dd, J_{vic}=4.5Hz, J_{gem}=12.4Hz); 4.66(1H, dd, J_{vic}=6.5Hz, J_{gem}=12.2Hz); 5.06(1H, 1/2ABq, J=12Hz); 5.14(1H, 1/2ABq, J=12Hz); 5.3(2H, t, broad); 7.1-7.4(10H, m). IR(NaCl, neat): 3050, 2980, 2920, 1735, 1700, 1415 cm^{-1}. Mass spectrum m/e = 397.3(M^+, 1%), 262 (14.5%).



^{1}H NMR (270 MHz) of **124b** in $CDCl_3$ at 295°K.



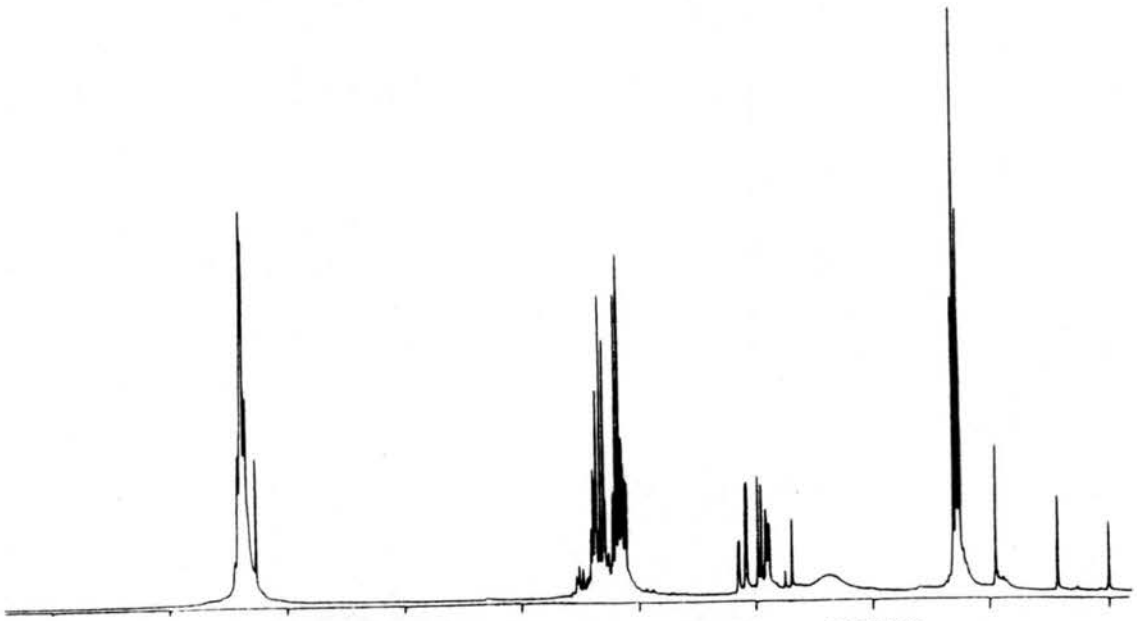
124 **126**

(5S)-3-((Ethoxycarbonyl)methyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (126)

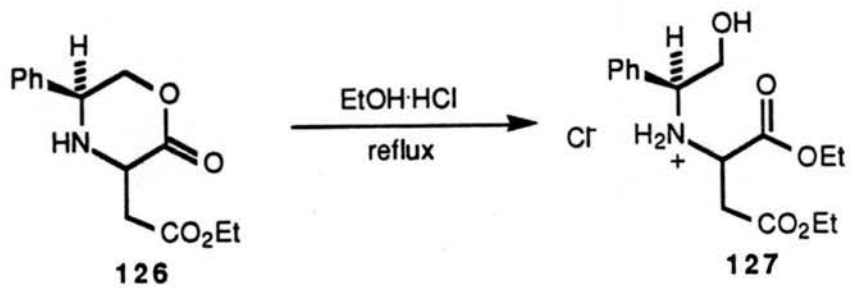
To a stirred solution of **124b** (91 mg, 0.23 mmol, 1 equiv) in absolute EtOH (3 mL) was added 10% Pd/C (37 mg, 0.03 mmol, 0.15 equiv). Hydrogen gas was bubbled

through the mixture for 40 min. The mixture was purged with N_2, filtered, and concentrated affording 55 mg (90%) **126** as a colorless oil.

^{1}H NMR (270 MHz)($CDCl_3$) δ $(CH_3)_4Si$: 1.28(3H, t, J=7.1Hz); 2.3(1H, s, broad); 2.89(1H, dd, J_{vic}=7.9Hz, J_{gem}=17.4Hz), 3.10(1H, dd, J_{vic}=3.2Hz, J_{gem}=17.4Hz); 4.1(1H, dd, J_{vic}=3.2Hz, J_{vic}=7.9Hz); 4.18(2H, q, J=7.1Hz); 4.32(3H, m); 7.15-7.25(5H, m). IR(NaCl, neat): 3330, 2925, 2850, 1734 cm^{-1}. Mass spectrum m/e = 263(M^+, 0.4%), 218(0.4%).



^{1}H NMR (270 MHz) of **125** in $CDCl_3$ at 295°K.



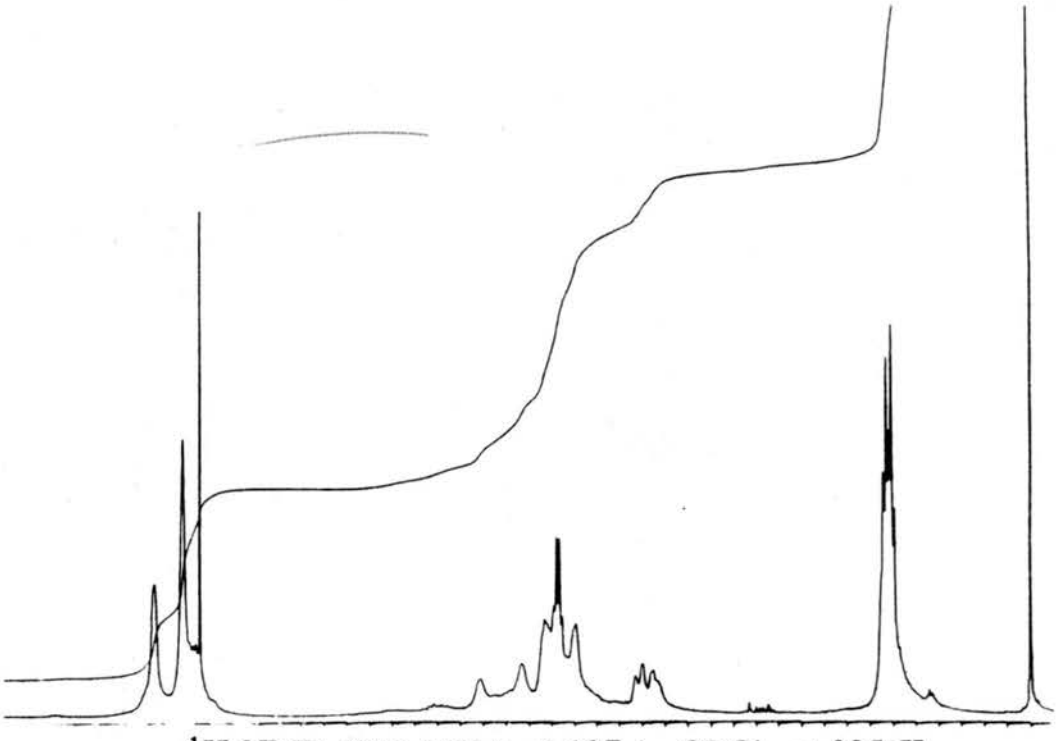
126 **127**

(1'S)-Diethyl-N-(2'-hydroxy-1'-phenylethyl)aspartate Hydrochloride (127)

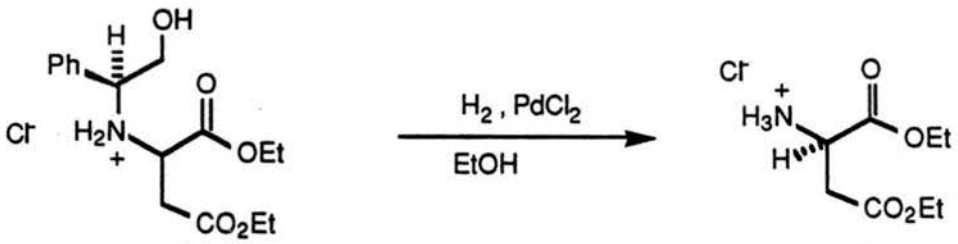
To a flask containing **126** (60 mg, 0.23 mmol, 1 equiv) was added EtOH·HCl (3 mL, approx. 3N) and the resultant mixture was refluxed for 1.5 hrs, cooled, and

concentrated in vacuo. The residue was dissolved in $CHCl_3$ and concentrated twice to remove HCl leaving 83.6 mg (106%) **127** as a yellow oil.

IR(NaCl, neat): 3400-3100, 3050, 2980, 2930, 1745, 1560, 1375, 1265, 1020 cm^{-1}.

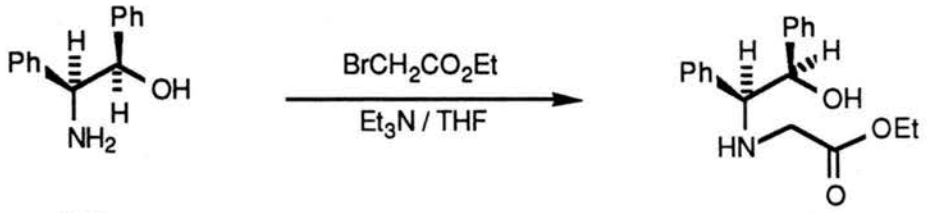


^1H NMR (270 MHz) of **127** in $CDCl_3$ at 295°K.



127 **139**

To a stirred solution of **127** (84 mg, 0.228 mmol, 1 equiv) in EtOH (1.5 mL) was added $PdCl_2$ (8 mg). The mixture was hydrogenated at 40 psi for 24 h. The mixture was purged with N_2, filtered through celite and concentrated. ^1H NMR analysis (D_2O) showed presence of diethyl aspartate **139**.

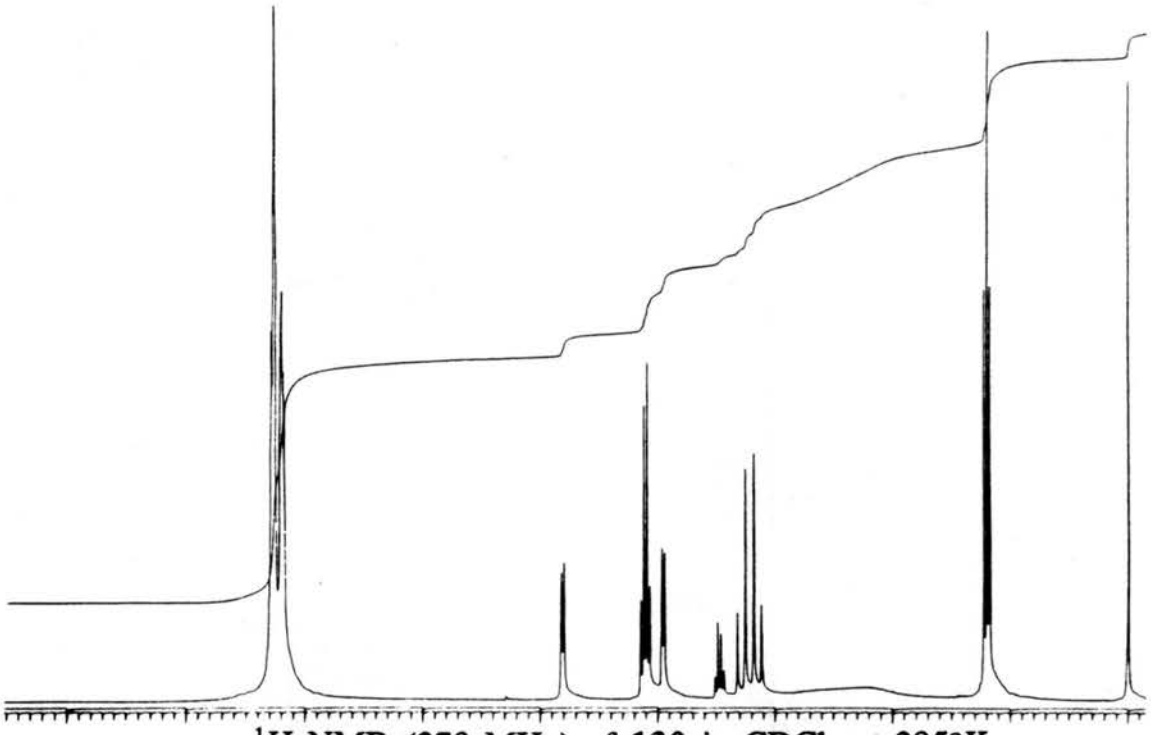


129a **130a**

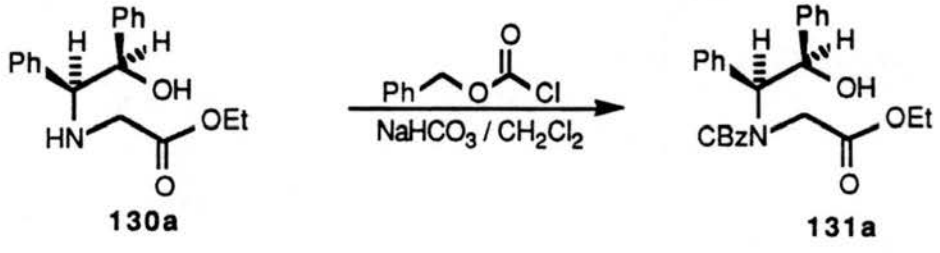
(1'R,2'S)-Ethyl-N-(1',2'-diphenyl-2'-hydroxyethyl)-glycinate (130)

To a suspension of **129a** (10 g, 46.95 mmol, 1 equiv) in dry THF (400 mL) was added ethylbromoacetate (5.9 mL, 51.64 mmol, 1.1 equiv) followed by addition of triethylamine (13 mL, 93.90 mmol, 2 equiv). After stirring 2 days the mixture was concentrated, diluted with CH_2Cl_2, passed over a silica gel plug, evaporated, and recrystallized (EtOAc/hexanes) to yield 8 g **130** as pure white crystals. The mother liquor was concentrated and the residue recrystallized to give 1.8 g **130** as pure white crystals. Combined yield 70%.

^1H NMR (270 MHz) ($CDCl_3$) δ ($CH_3)_4Si$: 1.20(3H, t, J=7.1Hz); 2.2(2H, broad s); 3.15(1H, 1/2ABq, J=17.5Hz); 3.29(1H, 1/2ABq, J=17.5Hz); 3.95(1H, d, J=6.0Hz); 4.11(2H, q, J=7.1Hz); 4.80(1H, d, J=6.0Hz); 7.17-7.32(10H, m). IR(NaCl, $CDCl_3$): 3840-3430, 3330, 3080, 3045, 2995, 2940, 1750, 1460, 1385, 1210, 1035, 915, 740 cm^{-1}. Analysis (recrystallized from EtOAc/hexanes) calculated for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.31; H, 7.16; N, 4.56, mp 126-127°C, $[\alpha]_D^{25}$ = -27.17 (c = 0.53, CH_2Cl_2).



^{1}H NMR (270 MHz) of **130** in $CDCl_3$ at 295°K.



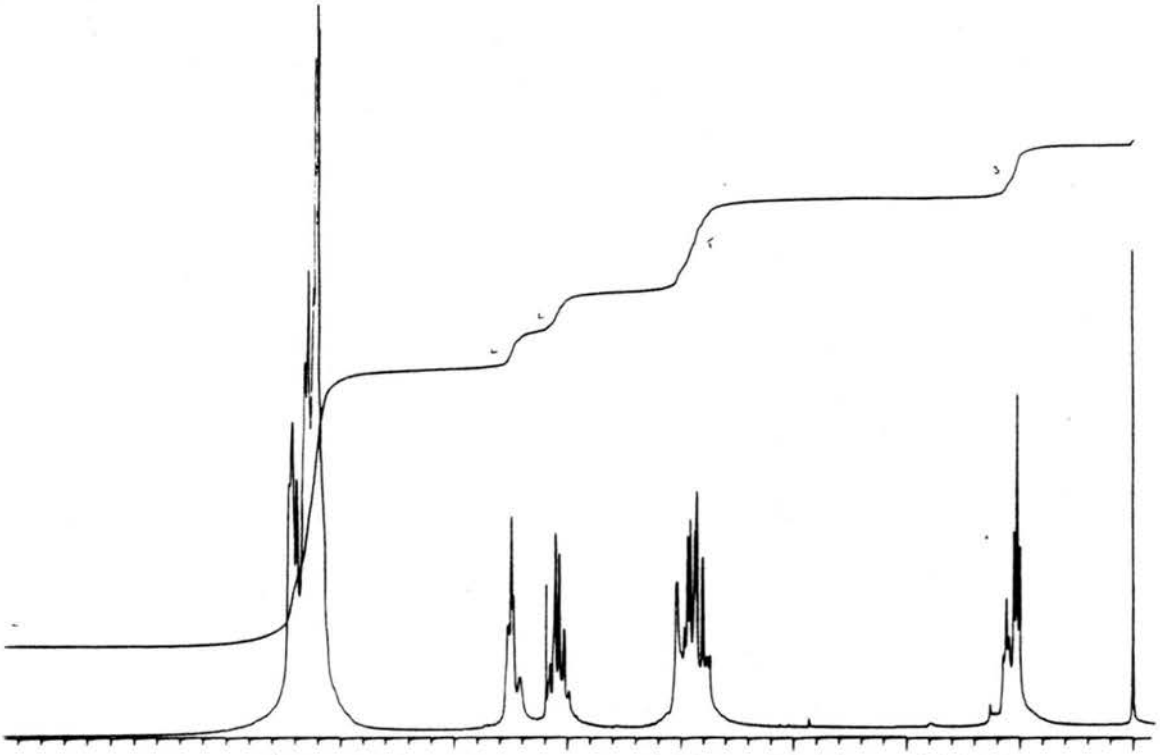
130a **131a**

(1'S,2'R)-Ethyl-N-benzyloxycarbonyl-N-(1',2'-diphenyl-2'-hydroxyethyl)-glycinate (131)

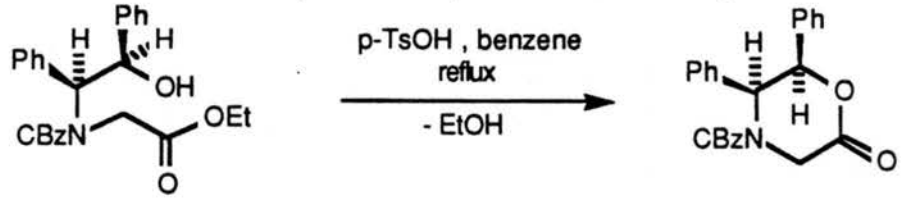
To a vigorously stirred mixture of **130** (8 g, 26.75 mmol, 1 equiv) in CH_2Cl_2 (150 mL) and saturated aqueous $NaHCO_3$ (150 mL) was added benzylchloroformate (4.42 mL, 29.43 mmol, 1.1 equiv). After stirring 6 h the aqueous layer was separated and extracted 3x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to give a colorless oil which was carried on crude.

^{1}H NMR (270 MHz) ($CDCl_3$) δ $(CH_3)_4Si$: 1.02(3H, t, J=7.1Hz); 3.7-4.0(5H, m); 4.98-5.18(2H, m); 5.42-5.53(2H, m); 7.1-7.5(15H, m). IR(NaCl, $CDCl_3$): 3450,

3060, 3035, 2980, 2900, 1755, 1700, 1500, 1455, 1400, 1190, 1120, 1025, 950, 910, 730, **695 cm^{-1}.**



^{1}H NMR (270 MHz) of **131** in $CDCl_3$ at 295°K.



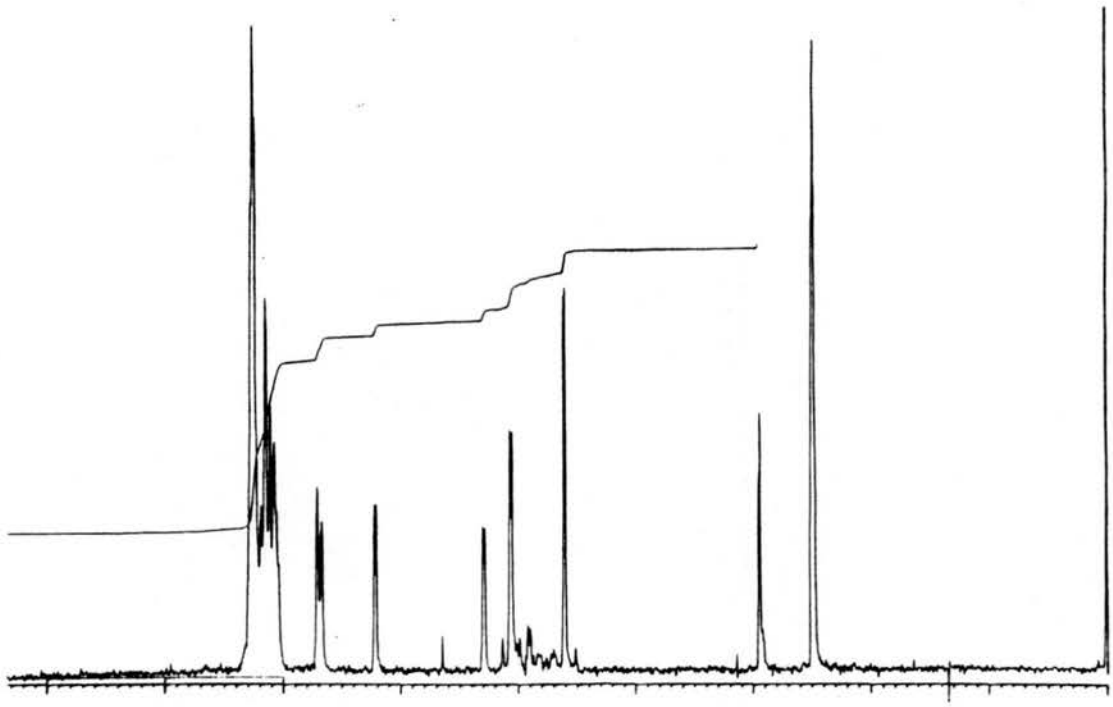
131a **108a**

(5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (108)

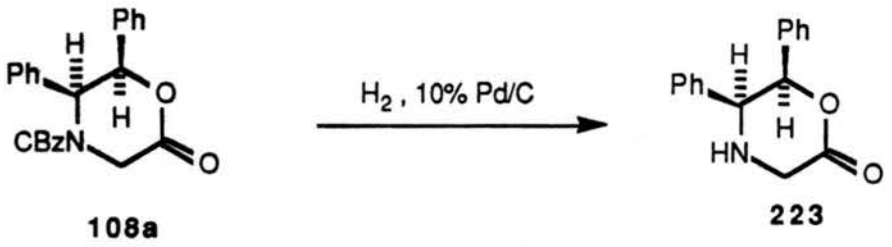
To a stirred solution of crude **131** (11.3 g, 26.75 mmol, 1 equiv) in benzene (450 mL) in a 1 liter 1-neck round bottom flask equipped with an empty Dean-Stark trap was added p-toluenesulfonic acid monohydrate (150 mg, 0.802 mmol, 0.03 equiv). The mixture was brought to reflux and approximately 300 mL of benzene was distilled off. The mixture was allowed to cool and the resultant precipitate was collected and recrystallized (benzene) to give 6.5 g **108** as a pure white solid. The mother liquors were combined,

concentrated and recrystallized (benzene/hexanes) to give 3.5 g **3** as pure white solid. Overall yield from **130** was 96%.

^{1}H NMR (200 MHz) (DMSO-d_6) (393°K) δ $(CH_3)_4Si$: 4.60(2H, ABq, J=17.6Hz); 5.06(2H, ABq, J=12.6Hz); 5.29(1H, d, J=3Hz); 6.20(1H, d, J=3Hz); 6.66(1H, s); 6.70(1H, s); 7.0-7.3(13H, m). IR(NaCl, paraffin oil): 1745, 1705, 1455, 1440, 1375, 1325, 1215, 1120, 1055 cm^{-1}. Analysis (racemic, recrystallized from CH_2Cl_2) calculated for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.61. Found: C, 73.85; H, 5.38; N, 3.5. For the D series lactone, mp 202-204°C, $[\alpha]_D^{25}$ = -66.7° (c = 0.815, CH_2Cl_2). For L-series lactone, mp 199.5-200.5°C, $[\alpha]_D^{25}$ = +66.94° (c = 0.62, CH_2Cl_2).



^{1}H NMR (200 MHz) of **108** in DMSO-d_6 at 393°K.

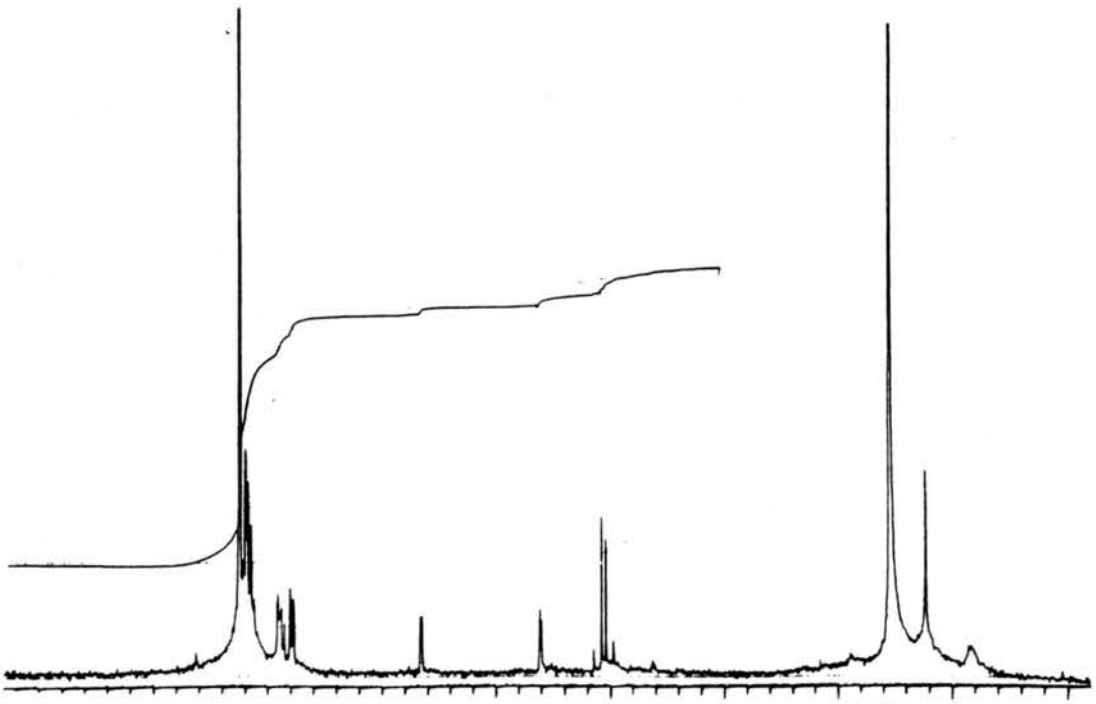


108a **223**

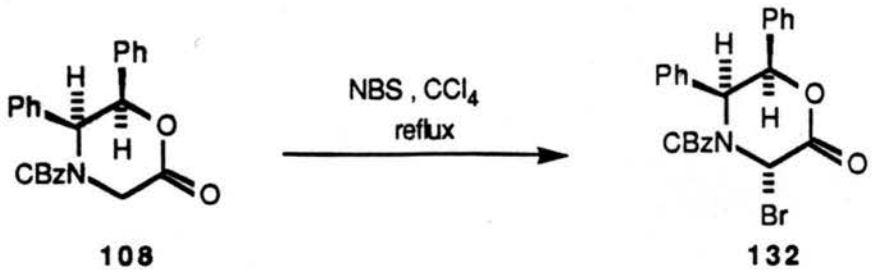
(5S,6R)-5,6-Diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (223)

To a stirred solution of **108** (7.5 mg, 0.019 mmol, 1 equiv) in dry THF (0.5 mL) was added 10% Pd/C (6 mg, 0.006 mmol, 0.3 equiv). Hydrogen was bubbled through. After 1.5 h the mixture was purged with nitrogen, filtered, concentrated and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 4.1 mg (80%) **223** as a colorless oil.

^{1}H NMR (270 MHz) ($CDCl_3$) δ ($CHCl_3$): 4.0(1H, 1/2ABq, J=18.3Hz); 4.1(1H, 1/2ABq, J=18.3Hz); 4.6(1H, d, J=3.8Hz); 5.6(1H, d, J=3.8Hz); 6.75-7.25(10H, m).



^{1}H NMR (270 MHz) of **223** in $CDCl_3$ at 295°K.

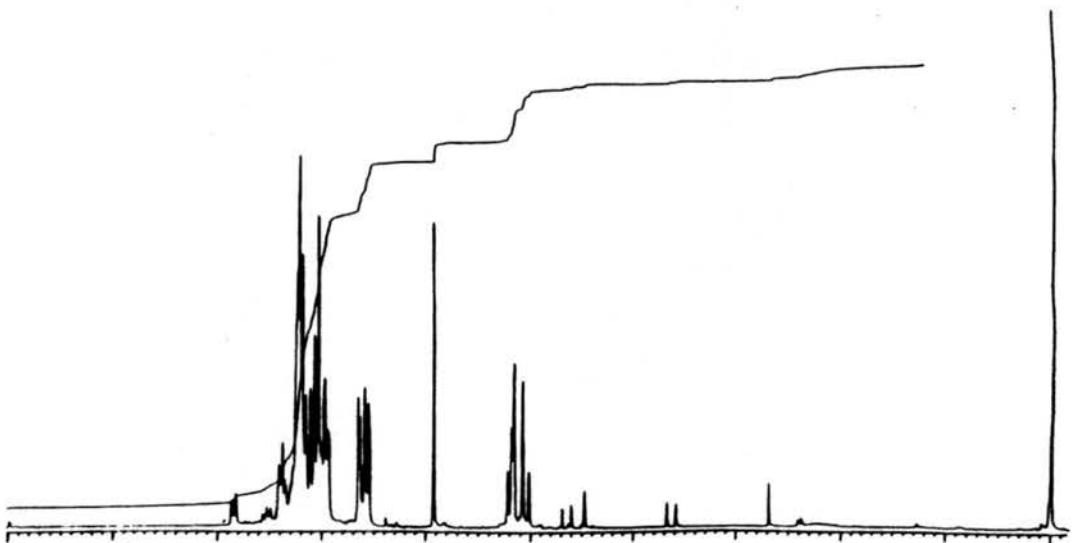


108 **132**

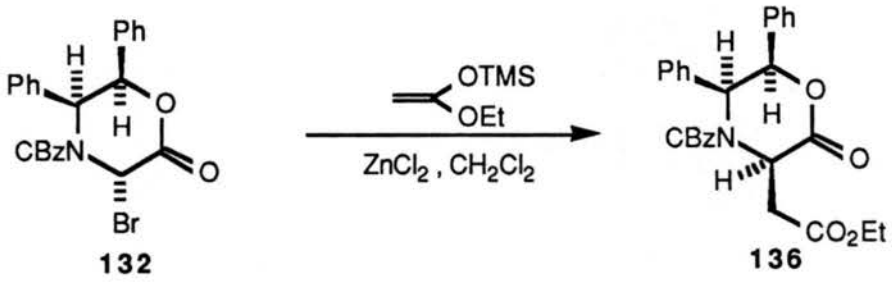
(3S,5S,6R)-4-Benzyloxycarbonyl-3-bromo-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (132)

A suspension of **108** (50 mg, 0.129 mmol, 1 equiv) in CCl_4 (15 mL) was brought to reflux. Upon complete dissolution of the oxazinone, NBS (27.6 mg, 0.155 mmol, 1.2 equiv) was added and the mixture was refluxed for an additional 45 min. The mixture was cooled to 0°C, filtered to remove succinimide, and concentrated to yield 60 mg (100%) **132** as a white solid.

^{1}H NMR (200 MHz) ($Cl_2CDCDCl_2$) (393°K) δ ($CH_3)_4Si$: 5.04(1H, 1/2ABq, J=12.2Hz); 5.19(1H, d, J=3.5Hz); 5.18(1H, 1/2ABq, J=12.2Hz); 6.55(1H, s); 6.58(1H, s); 6.62(1H, d, J=3.5Hz); 6.93-7.40(14H, m). IR(NaCl, neat): 3035, 1760, 1725, 1455, 1390, 1350, 1280, 1265, 1160, 1110 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 484.7(M^+ +18, .4%); 482.6(M^+ +18); 386.7(15.6%, M^+-80).



^{1}H NMR (200 MHz) 0f **132** in $Cl_2DCCDCl_2$ at 393°K.

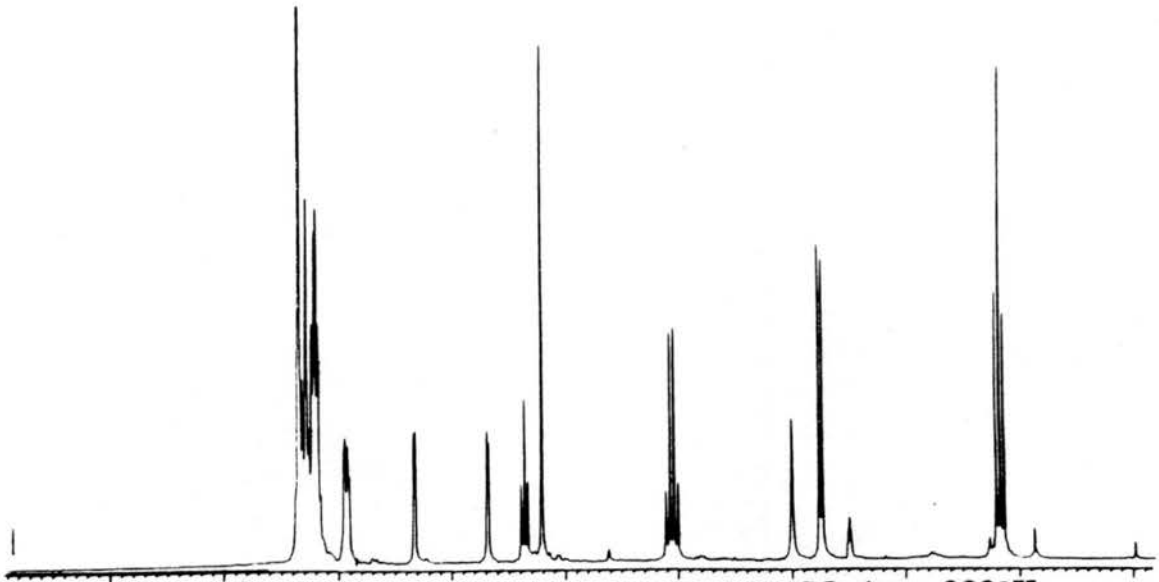


132 **136**

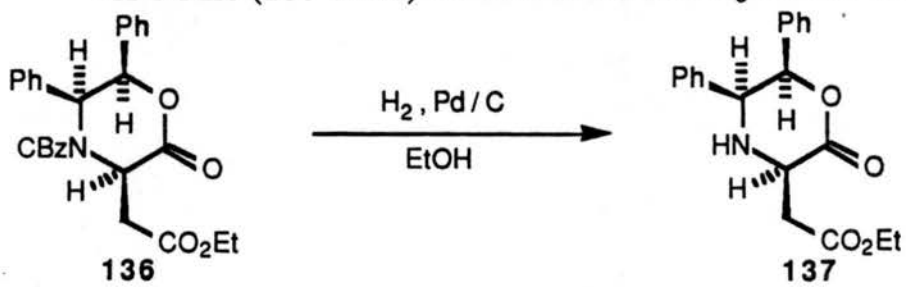
(3R,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-((ethoxycarbonyl)methyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (136)

To a stirred solution of **132** (226 mg, 0.48 mmol, 1 equiv) in CH_2Cl_2 (11 mL) was added ethylacetate t-butyldimethyl silyl ketene acetal (450 μL, 2.42 mmol, 5 equiv) followed by addition of $ZnCl_2$ (575 μL, 0.44 mmol, 0.9 equiv, 0.76M in THF). After 4 min the reaction was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford 179 mg (78%) **136** as a colorless oil.

^1H NMR (200 MHz) (DMSO-d_6) (380°k) δ $(CH_3)_4Si$: 1.15(3H, t, J=7.0Hz); 2.73(2H, d, J=5.8Hz); 4.04(2H, q, J=7.0Hz); 5.19(2H, s); 5.35(1H, t, J=5.8Hz); 5.67(1H, d, J=3.0Hz); 6.32(1H, d, J=3.0Hz); 6.88-6.93(2H, m); 7.16-7.32(13H, m). IR(NaCl, neat): 3060, 3030, 2980, 1730, 1700, 1400, 1370, 1290, 1240, 1215 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 491.6(M^+ +18, 0.7%), 472.6(M^+, 32.9%), $[\alpha]_D^{25}$ = +43.6 (c = 0.6, CH_2Cl_2).



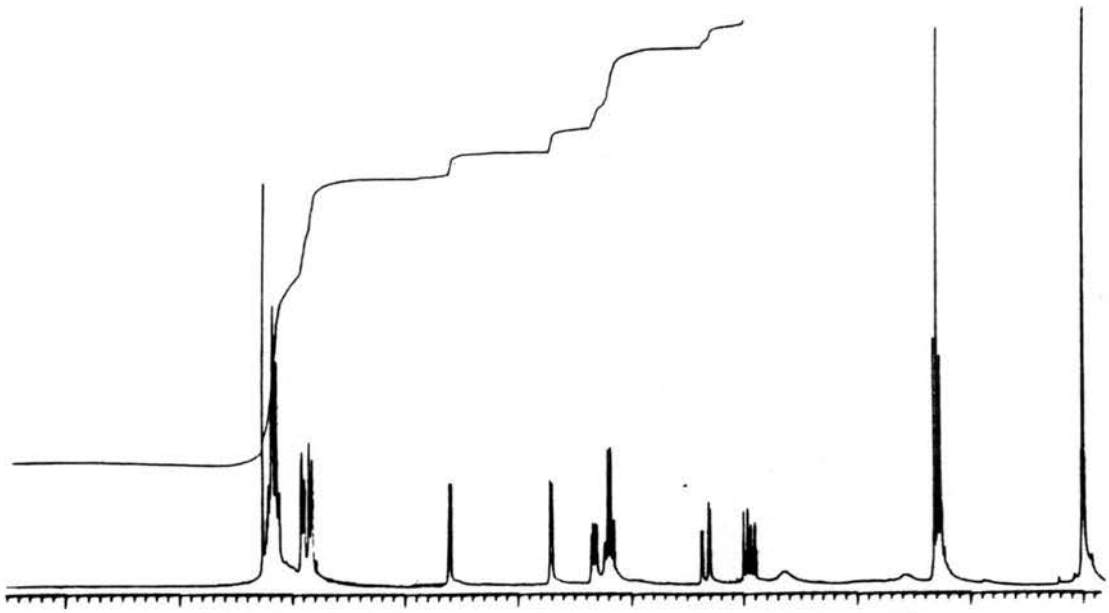
^{1}H NMR (200 MHz) of **136** in DMSO-d_6 at 393°K.



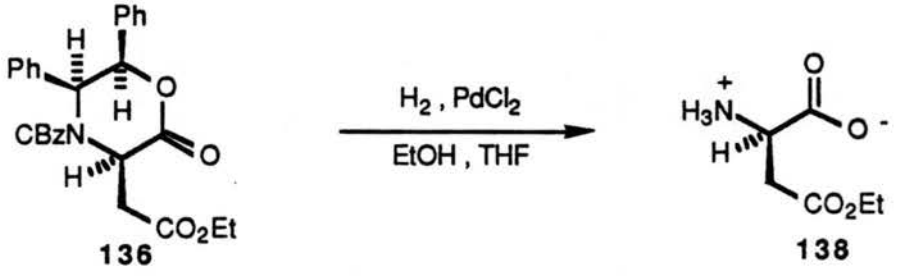
Racemic 5,6-Diphenyl-3-(ethylethonyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (137)

To a stirred solution of **136** (20 mg, 0.043 mmol, 1 equiv) in absolute ethanol (0.5 mL) was added 10% Pd/C (9 mg, 0.008 mmol, 0.20 equiv). Hydrogen was bubbled through the mixture. After 40 min, the mixture was purged with N_2, filtered and concentrated to give 15 mg (100%) **137** as a clear oil.

^{1}H NMR (270 MHz) ($CDCl_3$) δ $(CH_3)_4Si$: 1.29(3H, t, J=7.1Hz); 2.65(1H broad s); 2.95(1H, dd, J_{vic}=9.3Hz, J_{gem}=17.3Hz); 3.33(1H, dd, J_{vic}=3.1Hz, J_{gem}=17.3Hz); 4.19(2H, q, J=7.1Hz); 4.33(1H, dd, J_{vic}=3.1Hz, J_{vic}=9.3Hz); 4.70(1H, d, J=4.2Hz); 5.60(1H, d, J=4.2Hz); 6.8-7.2(10H, m). IR(NaCl, neat): 3050, 2980, 2920, 1735, 1370, 1260, 1170, 1015 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 338.9(M^+, 100%).



^{1}H NMR (270 MHz) of **137** ($ZnCl_2$ coupling) in $CDCl_3$ at 25°c.

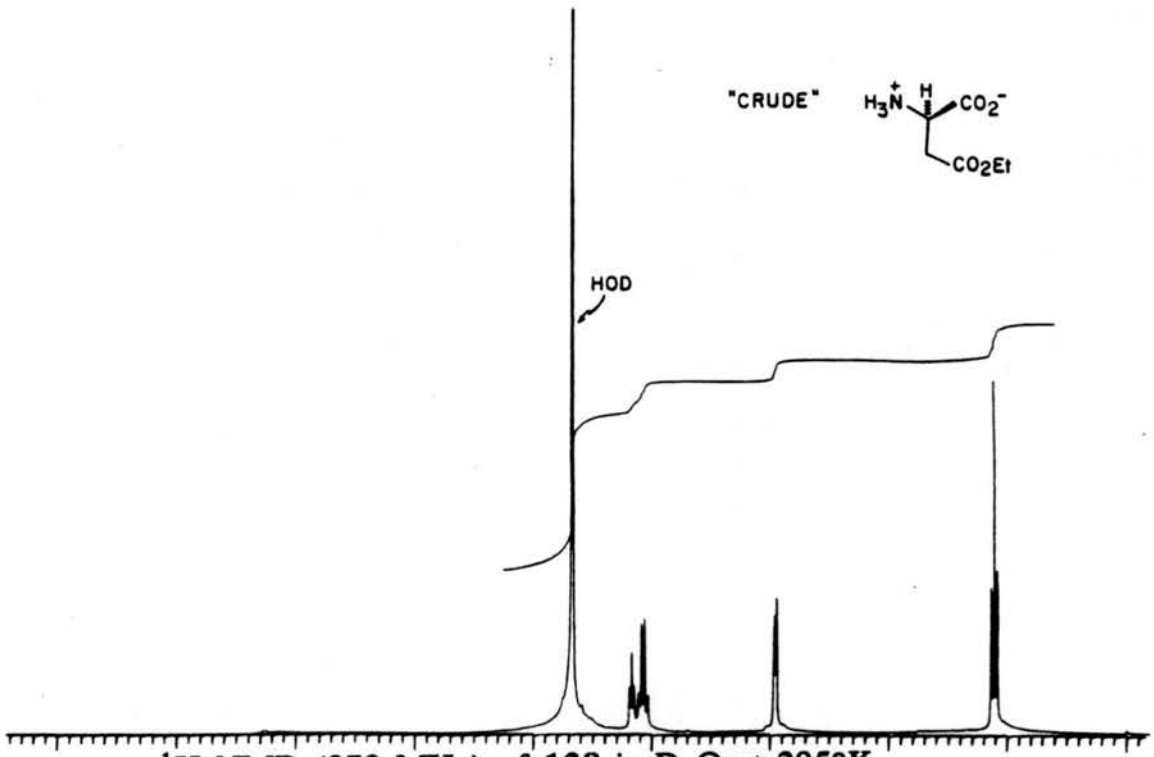


136 **138**

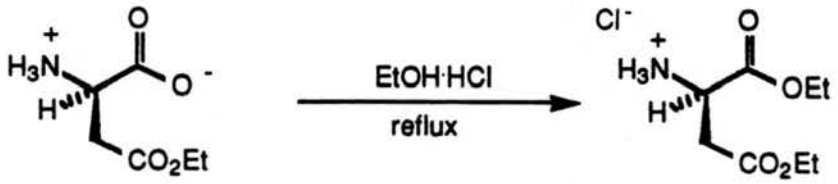
(R)-β-Ethyl Aspartate (138)

To a solution of **136** (86.5 mg, 0.18 mmol, 1 equiv) in THF (2 mL) plus absolute EtOH (2 mL) was added $PdCl_2$ (19 mg, 0.05 mmol, 0.3 equiv). The system was flushed with H_2 and hydrogenated at 20 psi for 24 hr at 25°C. The mixture was filtered through celite to remove catalyst concentrated, and triturated with Et_2O affording 34.2 mg (111%) **136** as a white powder.

^{1}H NMR (270 MHz)(D_2O) δ HOD: 1.11(3H, t, J=7.2Hz); 2.96(2H, d, J=5.1Hz); 4.08(2H, g, J=7.2Hz); 4.18(1H, t, J=5.6Hz). IR(KBr): 3250-2650, 1740, 1715, 1585, 1565, 1490, 1380, 1340, 1230, 1195 cm^{-1}.



^{1}H NMR (270 MHz) of **138** in D_2O at 295°K.



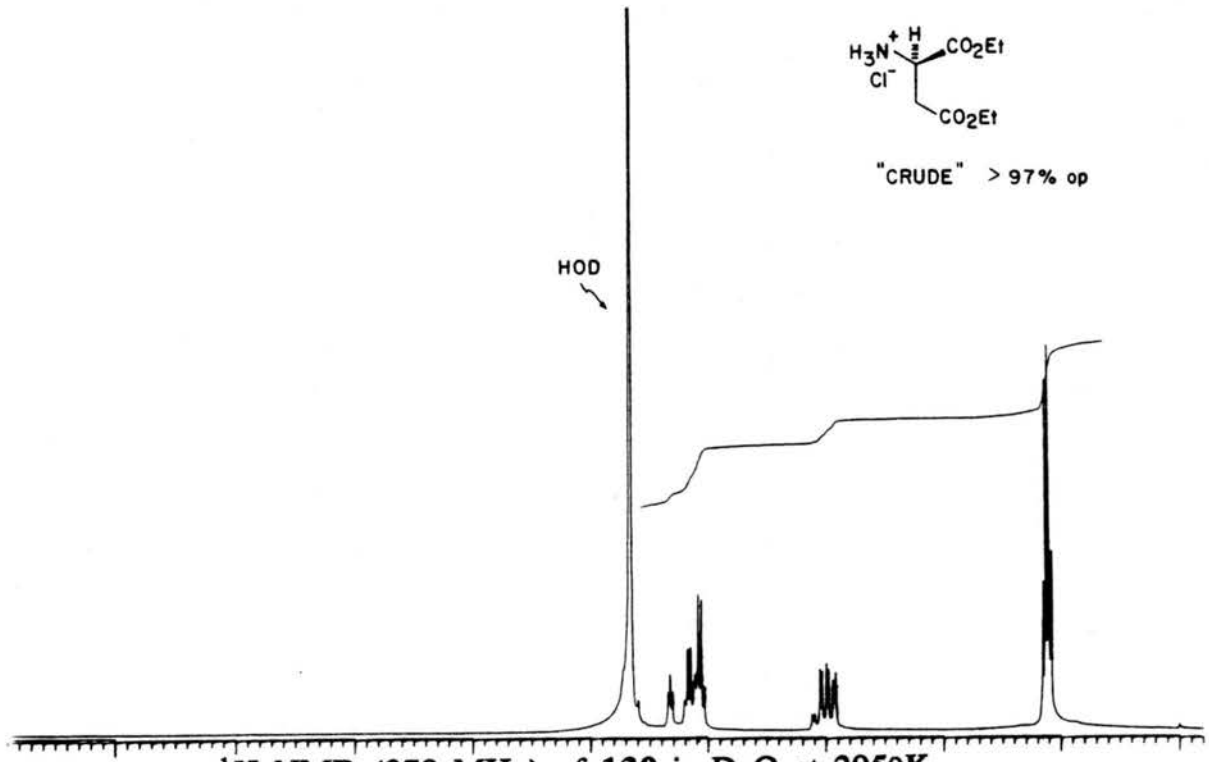
138 **139**

(R)-Diethylaspartate Hydrochloride (139)

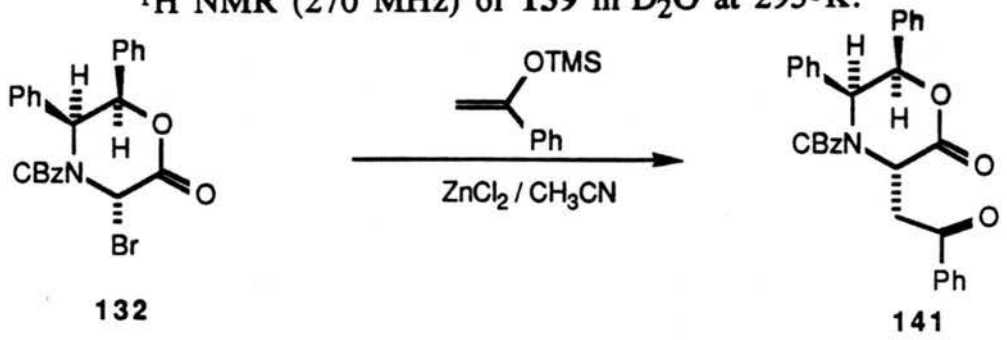
To a flask containing **138** (25 mg, 0.15 mmol, 1 equiv) was added EtOH·HCl (5 ml, 1N). The mixture was refluxed 1.5 hrs, cooled, concentrated and triturated (Et_2O, EtOAc) to afford **139** as a white solid, % ee ≥96 (Figure 19b).

^{1}H NMR (270 MHz) (D_2O) δ HOD: 1.12(3H, t, J=7Hz); 1.15(3H, t, J=7Hz); 2.90-3.13(2H, m); 4.08(2H, q, J=7Hz); 4.17(2H, q, J=7Hz); 4.33(1H, t, J=4Hz).

$[\alpha]_D^{25}$ = -7.4(c = 1, H_2O). Lit. (L) diethylaspartate·HCl = +7.6 (c = 1, H_2O).



^{1}H NMR (270 MHz) of **139** in D_2O at 295°K.



132 **141**

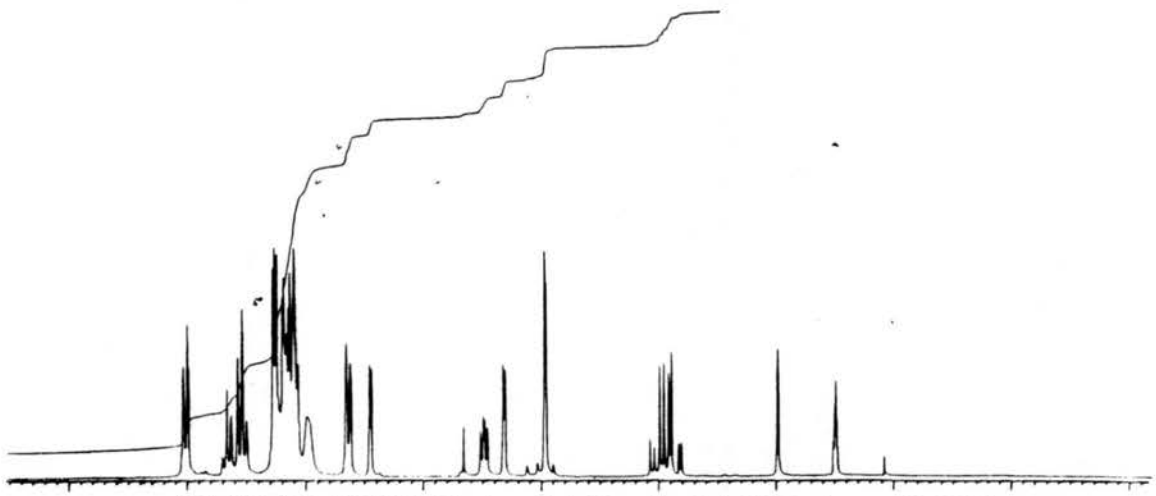
(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(2'-phenylethan-2-onyl)-2,3,5,6-tetrahydro-1,4-oxazine-2-one (141a) and (3R,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(2'-phenylethan-2-onyl)-2,3,5,6-tetrahydro-1,4-oxazine-2-one (141b)

To a stirred solution of **132** (300 mg, 0.65 mmol, 1 equiv) in CH_3CN (10 mL) was added the trimethylsilyl enol ether of acetophenone (265 μL, 1.29 mmol, 2 equiv) followed by addition of $ZnCl_2$ (5 mg, 0.04 mmol, 0.06 equiv). After 1.5 h all the bromide had dissolved. After an additional 45 min the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over

anhydrous sodium sulfate, filtered and concentrated. Crystallization from the crude mixture afforded 131 mg (40%) as a white solid. The mother liquor was concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 104 mg as a 5.8:1 mixture of diastereomers. Combined yield 72%.

(3S,5S,6R)-**141a**

^{1}H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 3.85(1H, dd, J_{vic}=4.4Hz, J_{gem}=16.5Hz); 4.00(1H, dd, J_{vic}=7.2Hz, J_{gem}=16.6Hz); 4.96(2H, s); 5.31(1H, d, J=3.1Hz); 5.48(1H, dd, J_{vic}=4.41Hz, J_{vic}=7.2Hz); 6.44(1H, d, J=3.1Hz); 6.61(1H, s); 6.62(1H, s); 6.65-7.27(13H, m); 7.49-7.66(3H, m); 7.99(1H, s); 8.03(1H, s). IR(NaCl, $CDCl_3$): 3065, 3030, 2915, 1745, 1700, 1600, 1580, 1500, 1450, 1400, 1345, 1275, 1215, 1175 cm^{-1}. Mass spectrum (NH_3)(CI): 505(M^+, 2.8%); 251(2.0%). Analysis (recrystallized EtOAc/hexanes) calculated for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 75.81; H, 5.49; N, 2.88. mp 200-201°, $[\alpha]_D^{25}$ = +5.25 (c = 1.2, CH_2Cl_2).

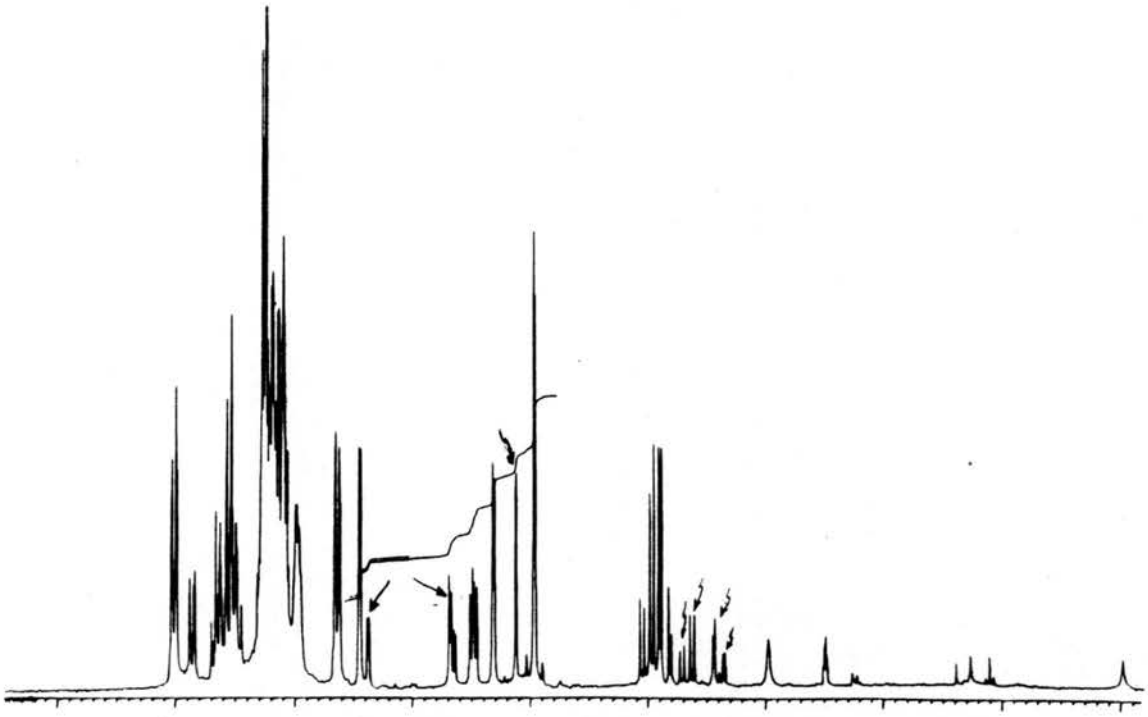


^{1}H NMR (200 MHz) of **141a** in DMSO-d_6 at 393°K.

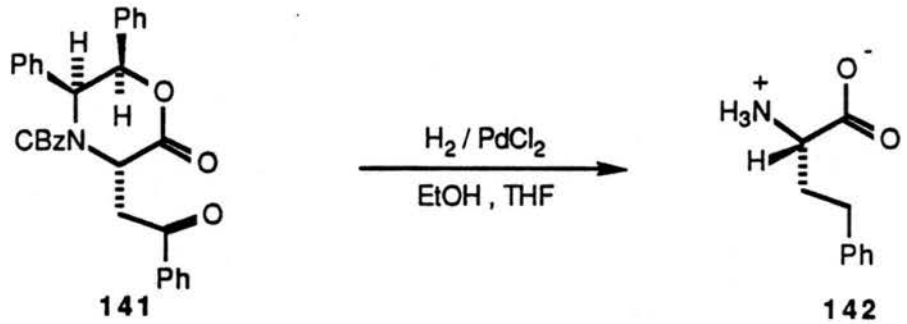
(3R,5S,6R)-**141b** (oil)

^{1}H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 3.39(1H, dd, J=3.1Hz, J=17.1Hz); 3.64(1H, dd, J=7.4Hz, J=17.1Hz); 5.12(2H, s); 5.64(1H, d, J=3.01Hz);

5.68(1H, d, J=3.2Hz); 6.37(1H, d, J=3.0Hz); 6.7(20H, m). IR(NaCl, neat): 3050, 2880, 1750, 1700, 1345, 1450, 1205, 1110 cm^{-1}. Mass spectrum (NH_3)(CI): 504.8(M^+, 0.1%), $[\alpha]_D^{25}$ = +46.4(c = 1.35, CH_2Cl_2).



^1H NMR (200 MHz) of **141b** in DMSO-d_6 at 393°K.

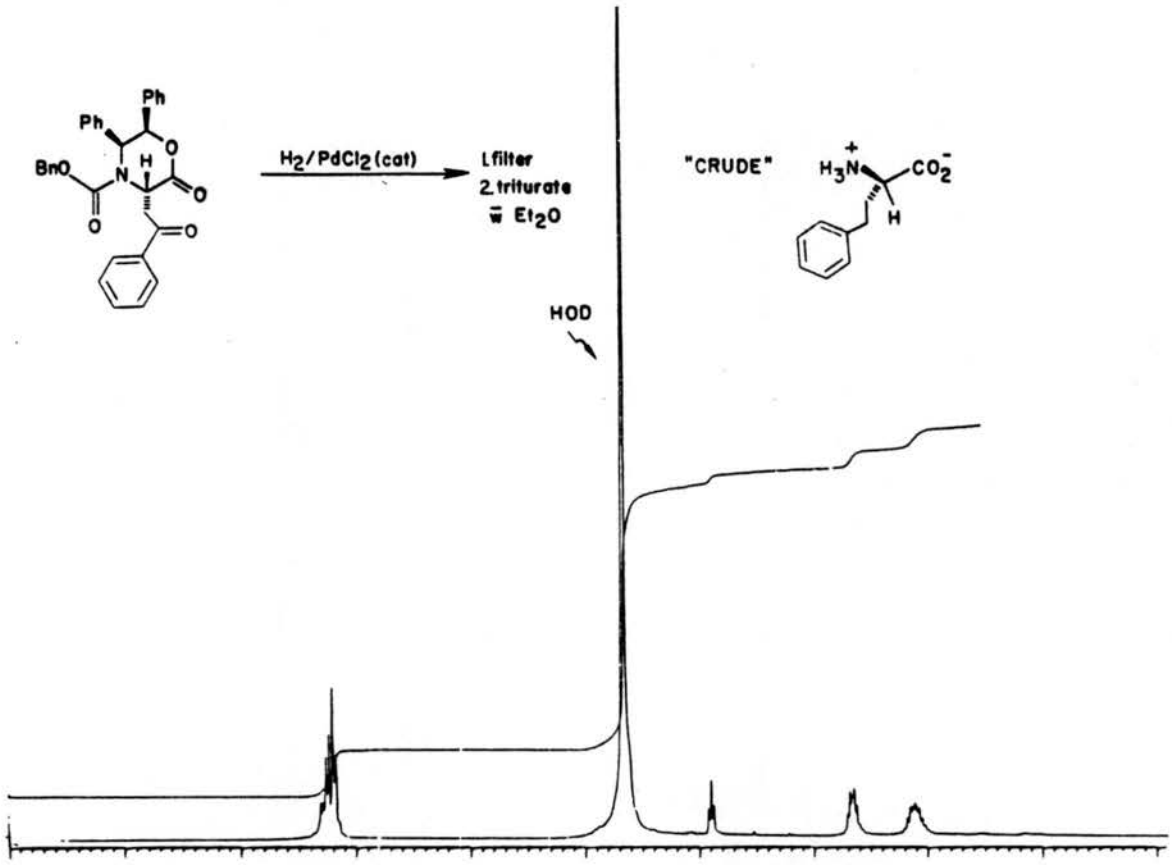


141 **142**

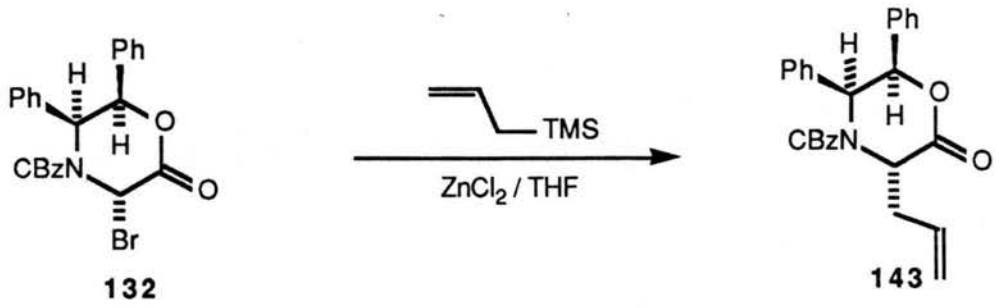
(S)-Homophenylalanine (142)

To a solution of 141 (133 mg, 0.263 mmol, 1 equiv) in 1:1 EtOH/THF (6 mL) was added $PdCl_2$ (27 mg, 0.079 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 34 h. The mixture was then purged with N_2, filtered through celite, concentrated to dryness, and triturated with Et_2O leaving 54 mg (114%) **142** as pure white solid, % ee ≥96 (Figure 20b).

IR(KBr): 2380-3300, 1735, 1600, 1495, 1450, 1210 cm^{-1}. $[\alpha]_D^{25}$ = -43 (c = 1, 1N HCl).



^1H NMR (270 MHz) of **142** in D_2O at 295°K.

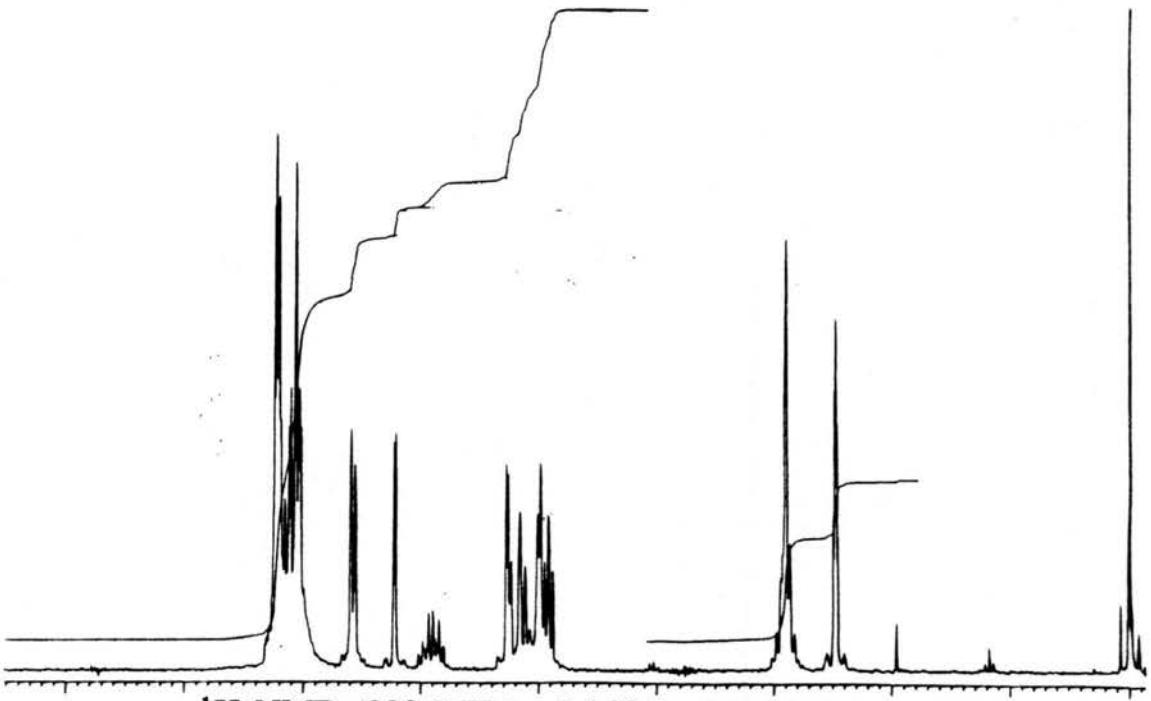


132 **143**

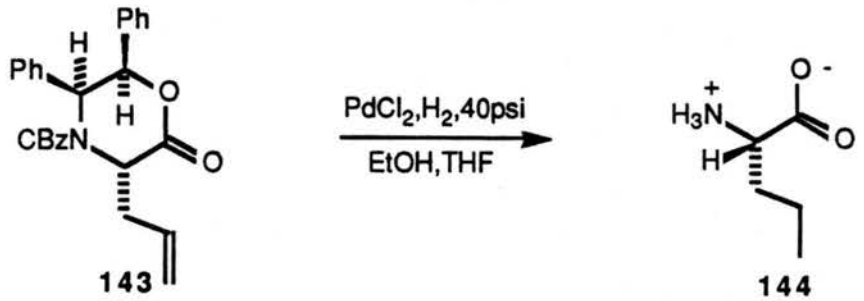
(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(2'-propenyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (143)

To a stirred solution of **132** (110 mg, 0.246 mmol, 1 equiv) in dry THF (2 mL) was added allyltrimethylsilane (150 μL, 0.944 mmol, 4 equiv) followed by addition of $ZnCl_2$ (2.5 mL, 0.472 mmol, 2 equiv, 0.187M in THF). After 60 h the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 68.3 mg (67.8%) **143** as a white solid.

^1H NMR (200 MHz) (DMSO-d_6) (396°K) δ $(CH_3)_4Si$: 2.9(2H, m); 4.92(1H, t, J=7Hz); 5.0(2H, ABq, J=13.2Hz); 5.17(2H, m); 5.27(1H, d, J=3.1Hz); 5.91(1H, m); 6.22(1H, d, J=3.1Hz); 6.59(1H, s); 6.63(1H, s); 7.0-7.35(13H, m). IR(NaCl, $CDCl_3$): 3095, 3075, 3045, 1760, 1700, 1500, 1450, 1400, 1345, 1310, 1295, 1280, 1240, 1210, 1185, 1115, 1080 cm^{-1}. Analysis (racemic, recrystallized EtOAc/hexanes) calculated for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.27. Found: C, 75.75; H, 5.97; N, 3.31, mp 165°C, $[\alpha]_D^{25}$ = -29.2 (c = 1.05, CH_2Cl_2).



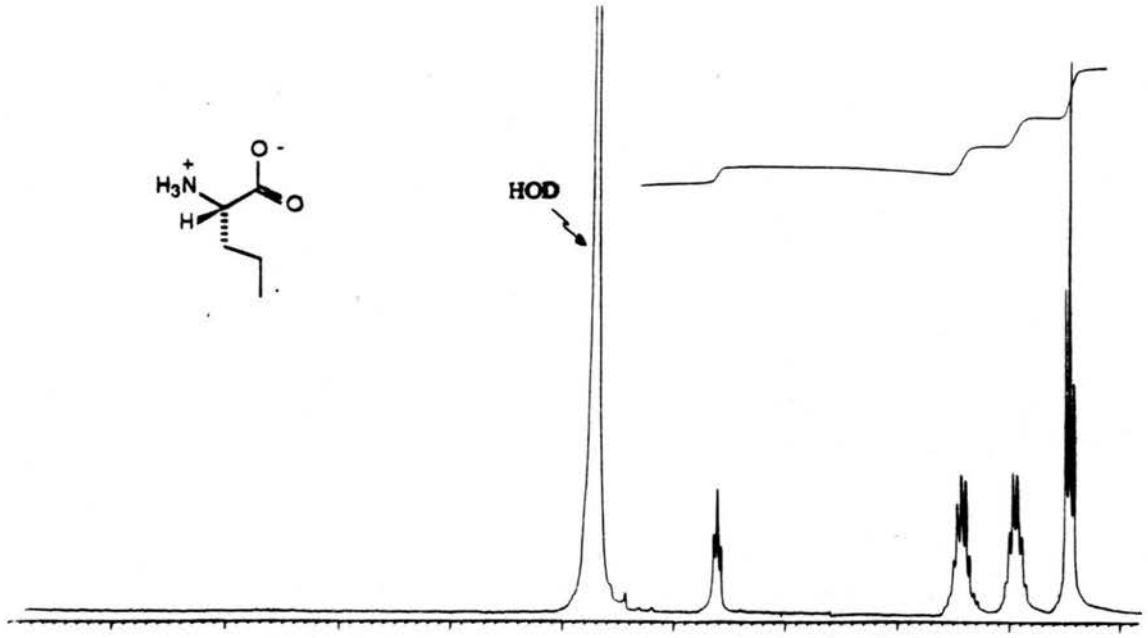
^{1}H NMR (200 MHz) of **143** in DMSO-d_6 at 393°K.



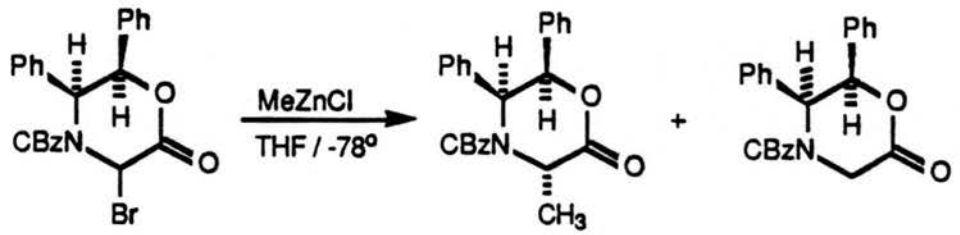
(S)-Norvaline (144)

To a stirred solution of **143** (115 mg, 0.27 mmol, 1 equiv) in absolute EtOH (2 mL) plus THF (2 mL) was added $PdCl_2$ (27 mg, 0.08 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 21 h. The mixture was filtered through celite to remove catalyst, concentrated, and triturated to give 42.4 mg (134%) **144** as a white powder, % ee ≥98 (Figure 21b).

^{1}H NMR (200 MHz) (1N DCl, D_2O) δ DSS: 0.95(3H, t, J=7.3Hz); 1.44(2H, m); 1.95(2H, m); 4.11(1H, t, J=6.1Hz). IR(KBr): 3620-3200, 2950, 2920, 2850, 1600(s), 1580, 1405, 1350 cm^{-1}. $[\alpha]_D^{25}$ = +15.96 (c = 1.04, 10% HCl).



^{1}H NMR (200 MHz) of **144** in D_2O/DCl at 295°K.

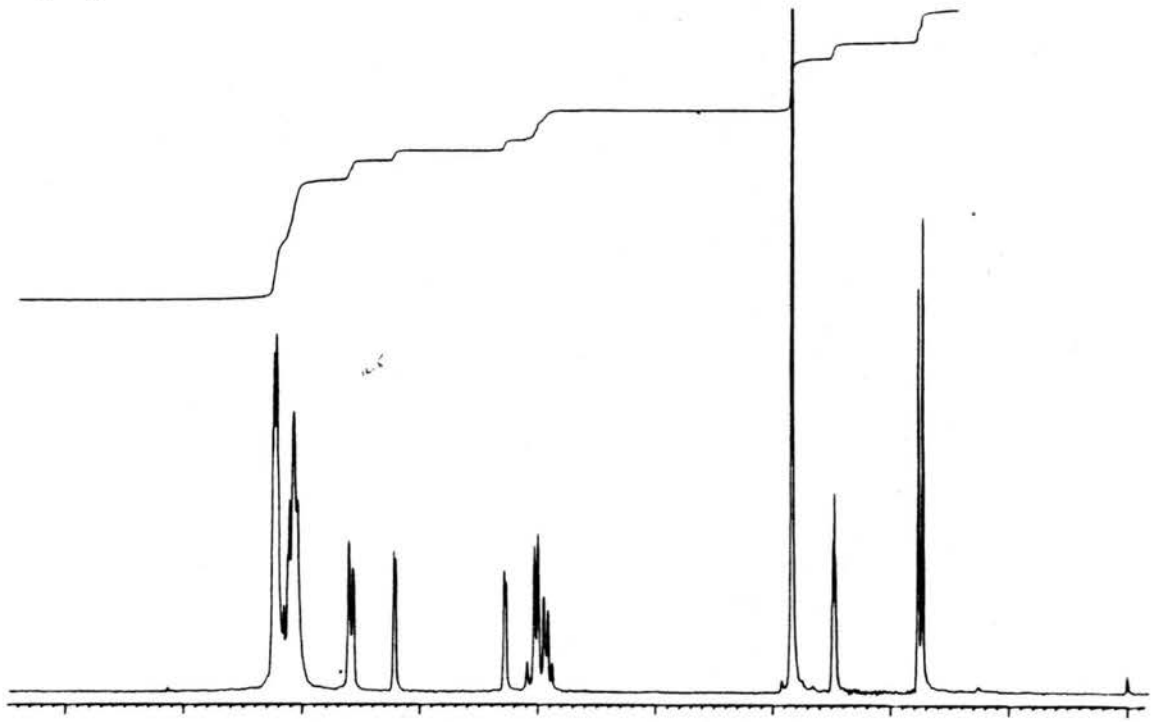


132 **145** **108**

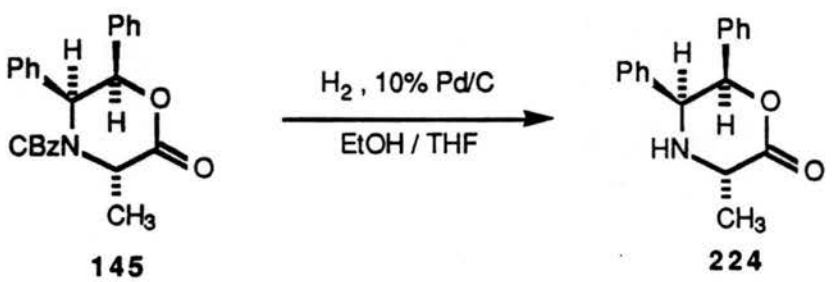
(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-1,4-oxazine-2-one (145)

To a stirred solution of **132** (301 mg, 0.643 mmol, 1 equiv) in dry THF (10 ml) at -78°C was added MeZnCl (2.6 mL, 2.2 equiv, 0.54M in THF) dropwise via syringe. After stirring 1 h at -78° the mixture was poured into water and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 91 mg (35%) **145** as a white solid and 37 mg (15%) **108** as white solid.

^{1}H NMR (200 MHz) (DMSO-d_6)(413°k) δ $(CH_3)_4Si$: 1.74(3H, d, J=7.2Hz); 4.92(1H, q, J=7.2Hz); 5.00(2H, ABq, J=12.7Hz); 5.28(1H, d, J=2.9Hz); 6.21(1H, d, J=2.9Hz); 6.56(1H, s); 6.59(1H, s); 7.03-7.24(13H). IR(NaCl, neat): 3060, 3030, 2950, 2930, 1760, 1705, 1500, 1455, 1400, 1350, 1285-1265, 1245, 1110, 1080 cm^{-1}. Analysis (recrystallized EtOAc/hexanes) calculated for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.52; H, 5.82; N, 3.48; mp 186-187°C, $[\alpha]_D^{25}$ = -50 (c = 1.04, CH_2Cl_2).



^{1}H NMR (200 MHz) of **145** in DMSO-d_6 at 413°K.



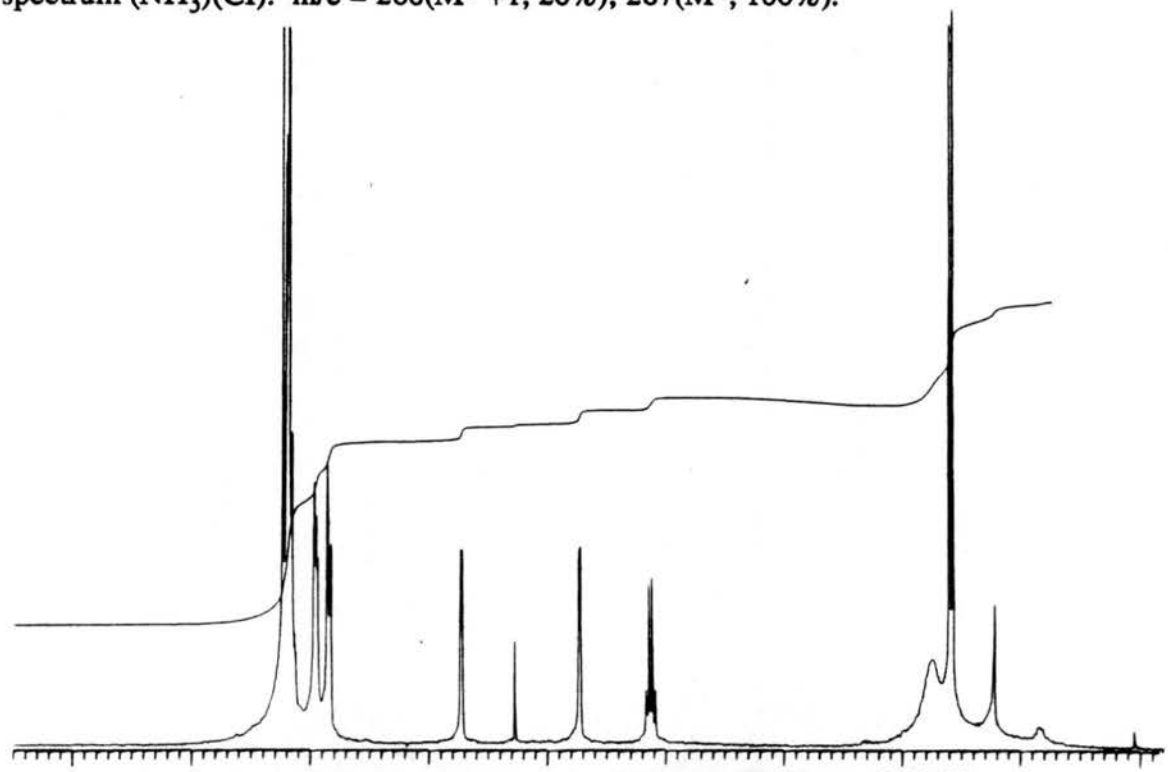
145 **224**

Racemic 5,6-Diphenyl-3-methyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (224)

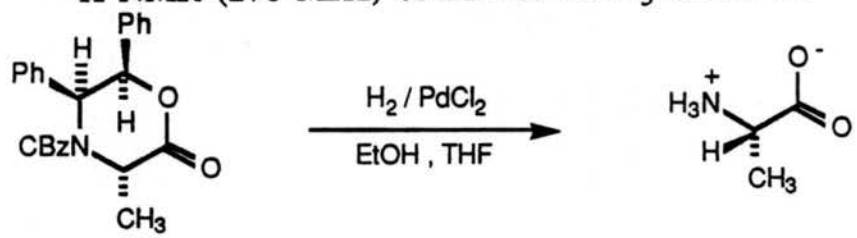
To a stirred solution of **145** (20 mg, 0.05 mmol, 1 equiv) in 1:1 EtOAc/THF (1 ml) was added 10% Pd/C (10.6 mg, 0.01 mmol, 0.2 equiv). H_2 was bubbled through the

mixture for 1 h. The reaction was purged with N_2, filtered, concentrated and separated on PTLC silica gel (eluted with 1:2 EtOAc/hexanes) to afford 5.7 mg (45%) **224** as an oil.

^{1}H NMR (270 MHz)($CDCl_3$) δ $CHCl_3$: 1.59(3H, d, J=7.1Hz); 1.67(1H, s, broad); 4.13(1H, q, J=7.1Hz); 4.73(1H, d, J=3.6Hz); 5.73(1H, d, J=3.6Hz); 6.8-7.4(10H, m). IR(NaCl, neat): 3050, 2980, 2920, 1735, 1445, 1260, 1200 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 268(M^+ +1, 20%); 267(M^+, 100%).



^{1}H NMR (270 MHz) of **224** in $CDCl_3$ at 295°K.



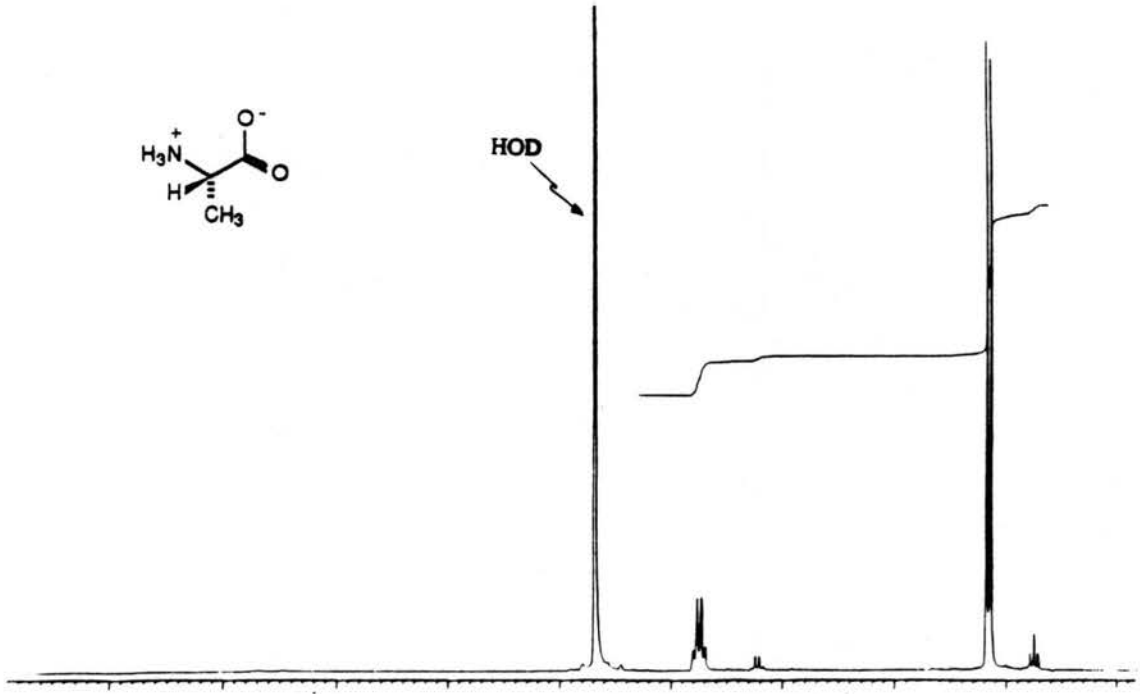
145 **147**

(S)-Alanine (147)

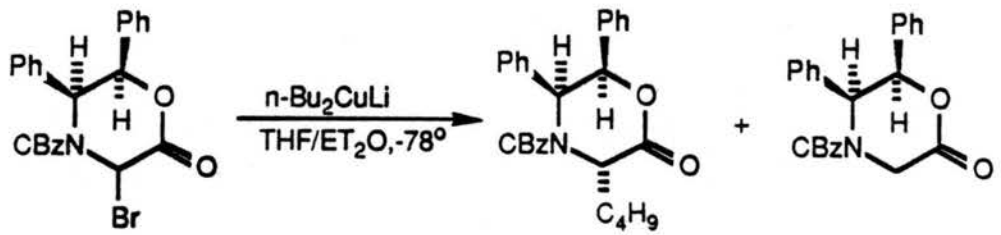
To a stirred solution of **145** (88 mg, 0.219 mmol, 1 equiv) in 1:1 absolute EtOH/THF (3 mL) was added $PdCl_2$ (22.3 g, 0.065 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 36 h. The mixture was purged with N_2, filtered through celite

to remove the catalyst concentrated in vacuo, and triturated with Et_2O leaving 23 mg (117%) **147** as a white powder, % ee ≥96 (Figure 22b).

^{1}H NMR (200 MHz)(~1N DCl, D_2O) δ DSS: 1.18(3H, d); 3.75(1H, q). IR(KBr): 3600-2200, 1605, 1570, 1435, 1395, 1345, 1285, 1090, 990 cm^{-1}. $[\alpha]_D^{25}$ = +2.1 (c = 0.37, H_2O).



^{1}H NMR (200 MHz) of **147** in D_2O/DCl at 295°K.



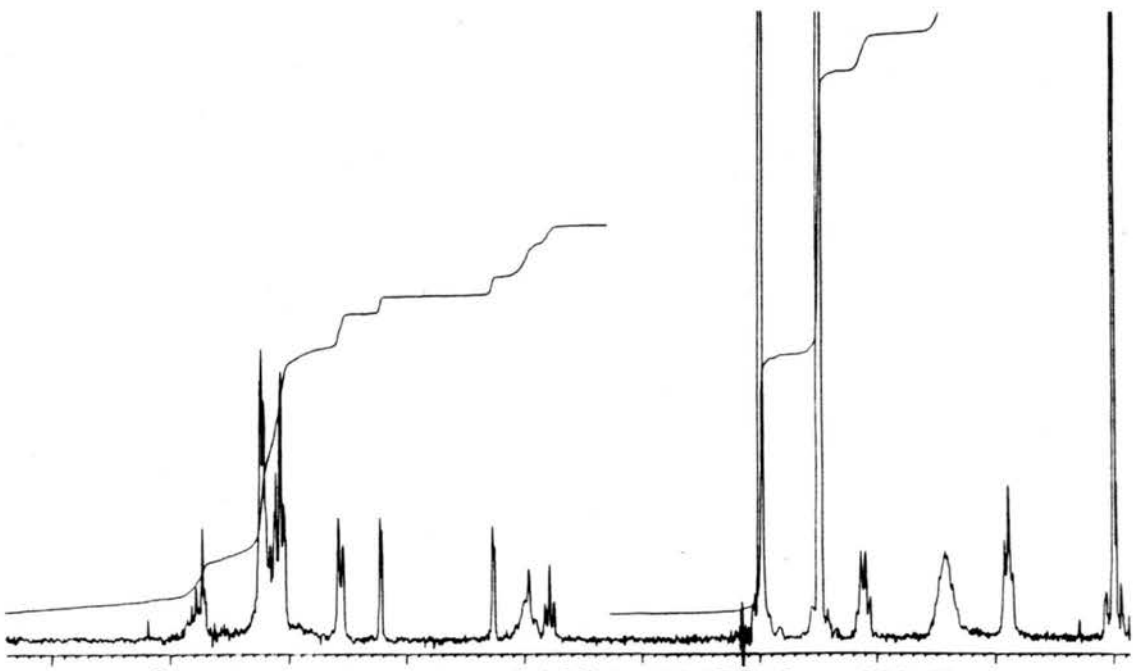
132 **146** **108**

(3S,5S,6R)-4-Benzyloxycarbonyl-3-butyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (146)

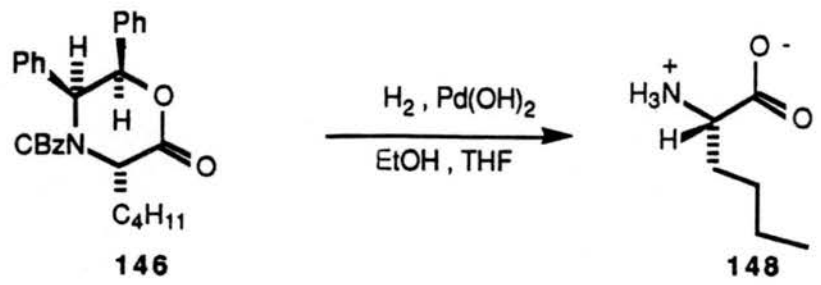
To a stirred suspension of CuCN (116 mg, 1.292 mmol, 2 equiv) in dry Et_2O (10 mL) was added nBuLi (1.55 mL, 2.454 mmol, 3.8 equiv) via syringe. The flask was

lifted above the surface of the cooling bath for 5 min to facilitate dissolution of the CuCN. The solution of the cuprate was then cooled to -78°C and transferred via cannula to a flask containing a solution of **132** (301 mg, 0.6459 mmol, 1 equiv) in dry 1:1 THF/Et_2O (20 mL) stirring at -78°C. After 50 min the reaction was quenched at -78°C by addition of saturated aqueous NH_4Cl. The mixture was extracted 4x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 82 mg (28%) **146** as a white solid and 69 mg (28%) **108** as a white solid.

^1H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 0.90(3H, broad t, J=6.6Hz); 1.43(4H, m); 2.12(2H, broad q, J=7.4Hz); 4.80(1H, t, J-7.3Hz); 4.97(2H, m); 5.28(1H, d, J=2.8Hz); 6.22(1H, d, J=2.8Hz); 6.55(1H, s); 6.58(1H, s); 7.00-7.25(13H, m). IR(NaCl, $CDCl_3$): 3060, 3025, 2950, 2920, 2860, 1745, 1700, 1490, 1460, 1445, 1390, 1335, 1315, 1305, 1290, 1275, 1260, 1230, 1175, 1100, 1070, 1050 cm^{-1}. Mass spectrum (NH_3)(CI): 461.2(M^+ +18, 6.5%); 443.3(M^+, 8.4%). Analysis (recrystallized from EtOAc/hexanes) calculated for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.86; H, 6.63; N, 3.17, mp = 160°, $[\alpha]_D^{25}$ = -46.0 (c = 0.76, CH_2Cl_2).



^1H NMR (200 MHz) of **146** in DMSO-d_6 at 393°K.

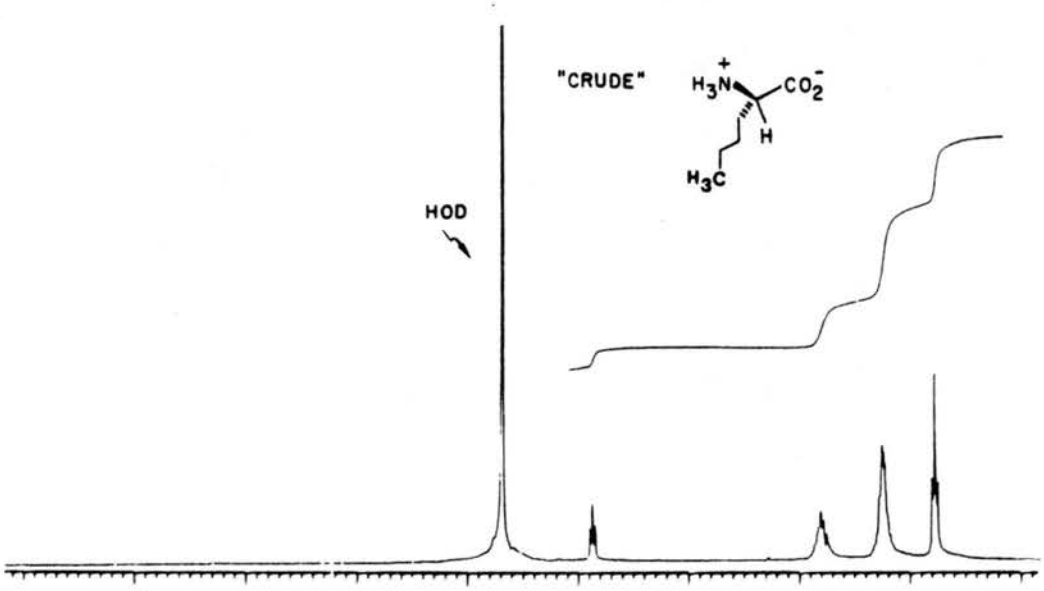


146 **148**

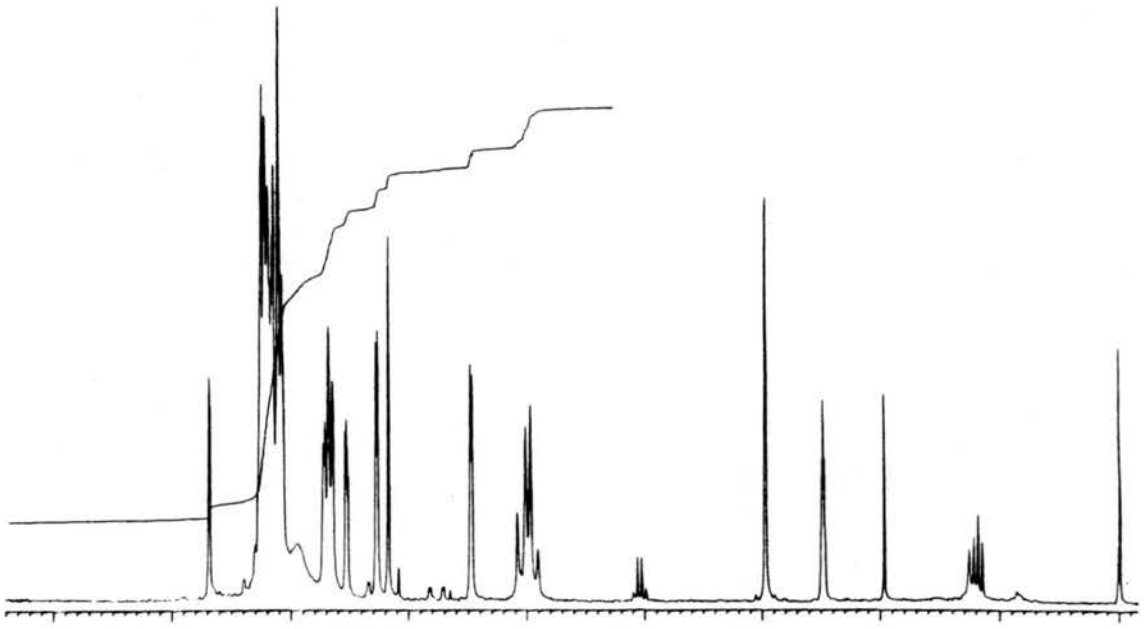
(S)-Norleucine (148)

To a stirred solution of **146** (82.3 mg, 0.186 mmol, 1 equiv) in 1:1 EtOH/THF (3 mL) was added 20% $Pd(OH)_2$ on carbon (39 mg, 0.0557 mmol, 0.3 equiv). The mixture was hydrogenated for 36 h at 30 psi. The mixture was then purged with N_2, filtered through celite to remove the catalyst, concentrated and triturated with Et_2O to yield 12.6 mg (52%) **148** as pure white solid, % ee ≥98 (Figure 23b).

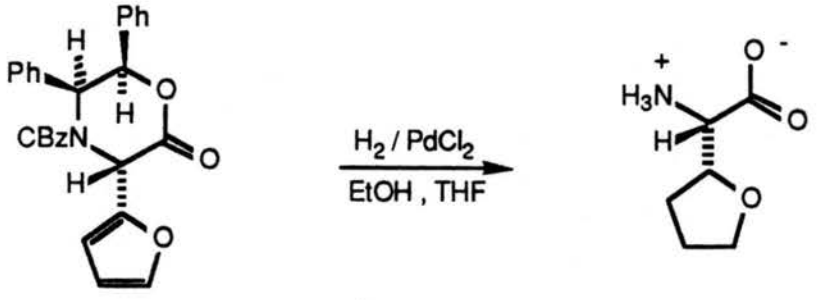
IR(KBr): HCl salt: 2700-3250, 1740, 1590, 1210 cm^{-1}. $[\alpha]_D^{25}$ = +16.12 (c = 0.67, 10% HCl).



^1H NMR (270 MHz) of **148** in D_2O at 295°K.



^{1}H NMR (200 MHz) of **149** in DMSO-d_6 at 393°K.



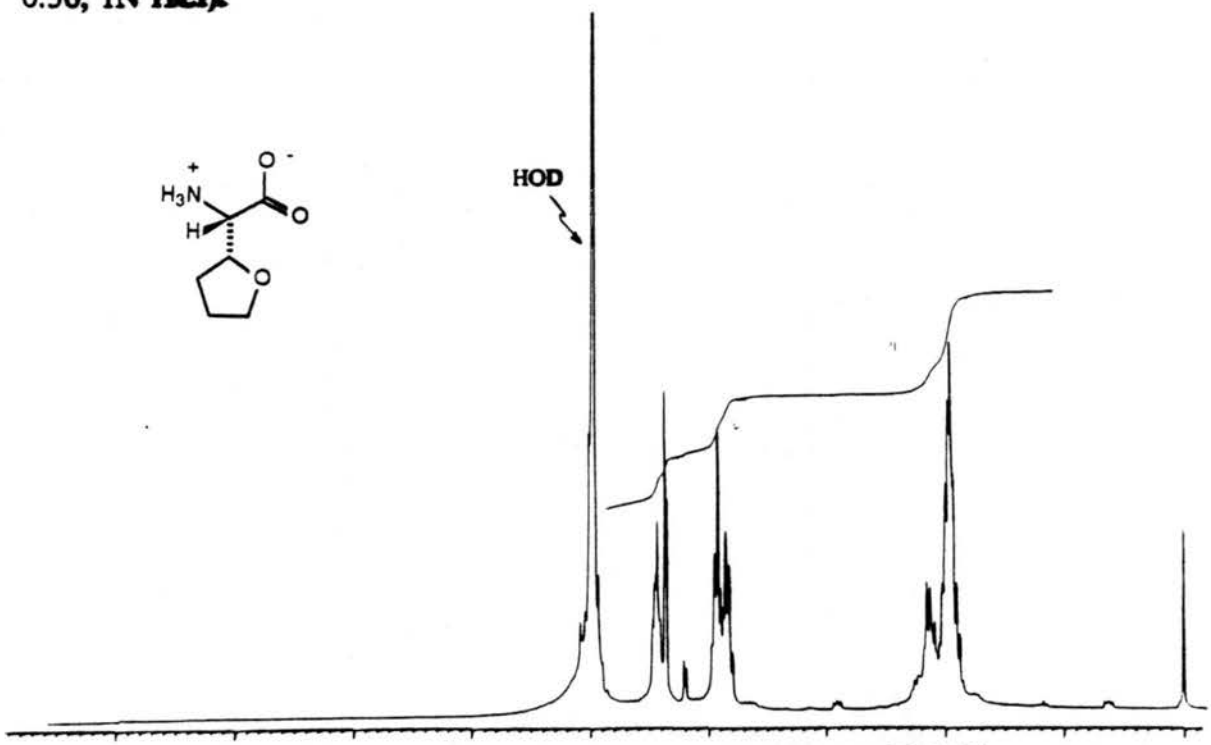
149 **151**

(2'-Tetrahydrofuryl)glycine (151)

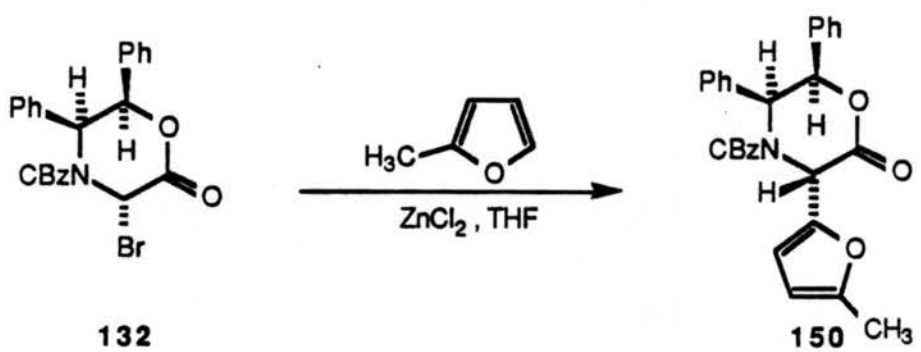
To a solution of **149** (100 mg, 0.27 mmol, 1 equiv) in 1:1 EtOH/THF (4 mL) was added $PdCl_2$ (22 mg, 0.07 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 30 h, purged with N_2, filtered through celite, and concentrated to dryness. The residue was dissolved in a minimum amount of EtOH and precipitated with Et_2O yield 35 mg (109%) **151** as approximately a 5:1 mixture of diastereomers obtained as a white solid..

^{1}H NMR (200 MHz)(D_2O + DCl) δ DSS: 1.8-2.2(4H, m); 3.79-3.97(2H, m); 4.36(major diastereomer 1H, d, J=3.9Hz); 4.40-4.46(1H, m). IR(KBr): 3600-3300,

3200-2800, 1620, 1590, 1550, 1515, 1400, 1350, 1315, 1055 cm^{-1}. $[\alpha]_D^{25}$ = +4.4 (c = 0.36, 1N HCl).



^1H NMR (200 MHz) of **151** in D_2O/DCl at 295°K.



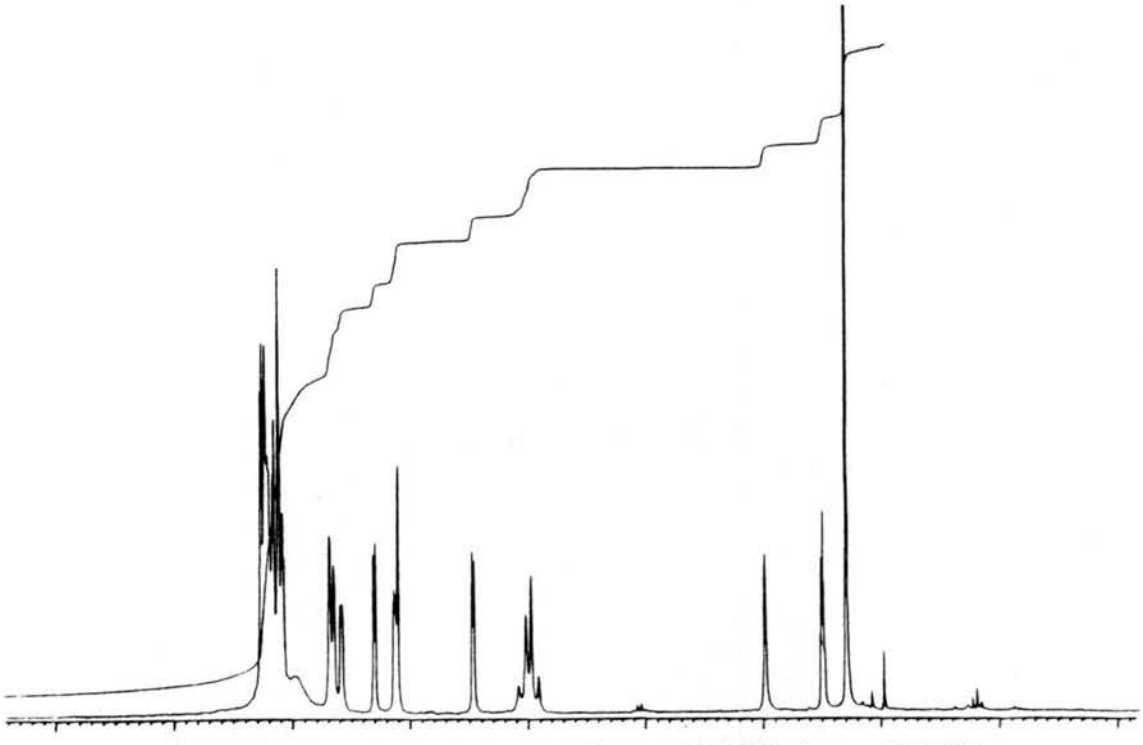
132 **150**

(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-[2'-(5'-methyl)-furyl-2,3,5,6-tetrahydrofuryl-1,4-oxazin-2-one (150)

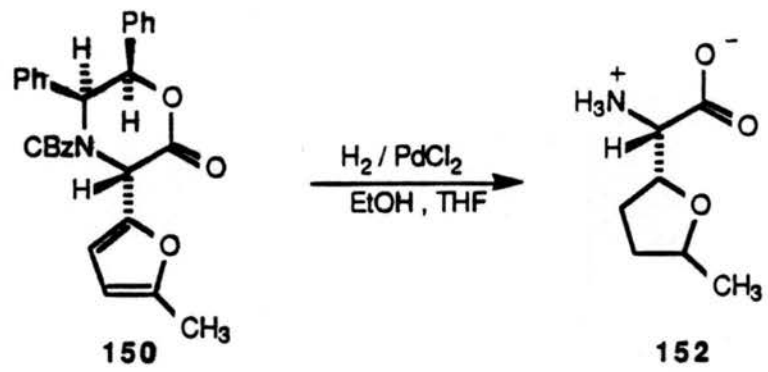
To a stirred solution of **132** (300 mg, 0.6459 mmol, 1 equiv) in dry THF (5 mL) was added 2-methylfuran (1 mL, 10.0731 mmol, 15.6 equiv) followed by addition of $ZnCl_2$ (650 µL, 1.2919 mmol, 2 equiv, 2M in THF). After 1.5 h, the mxiture was poured into water and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over

anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 200 mg (66%) **150** as a white solid.

^{1}H NMR (200 MHz)(DMS-d_6)(393°K) δ DMSO: 2.29(3H, s); 4.99(2H, ABq, J=12.6Hz); 5.46(1H, d, J=3.0Hz); 6.10(1H, s); 6.13(1H, m); 6.30(1H, d, J=3.0Hz); 6.58(1H, d, J=2.9Hz); 6.65(1H, s); 6.68(1H, s); 6.9-7.3(13H, m). IR(NaCl, CH_2Cl_2): 3030, 2980, 1765, 1710, 1455, 1395, 1260, 1110, 1084, 1055, 1020 cm^{-1}. Mass spectrum (NH_3)(CI): 485(M^+ +18, 41%); 467.2(M^+, 78.3%); 251.9(18.7%). Analysis (recrystallized from EtOAc/hexanes) calculated for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.20; N, 2.99. Found: C, 74.46; H, 5.26; N, 2.98, mp 171-172°, $[\alpha]_D^{25}$ = +44.7 (c = 1.09, CH_2Cl_2).



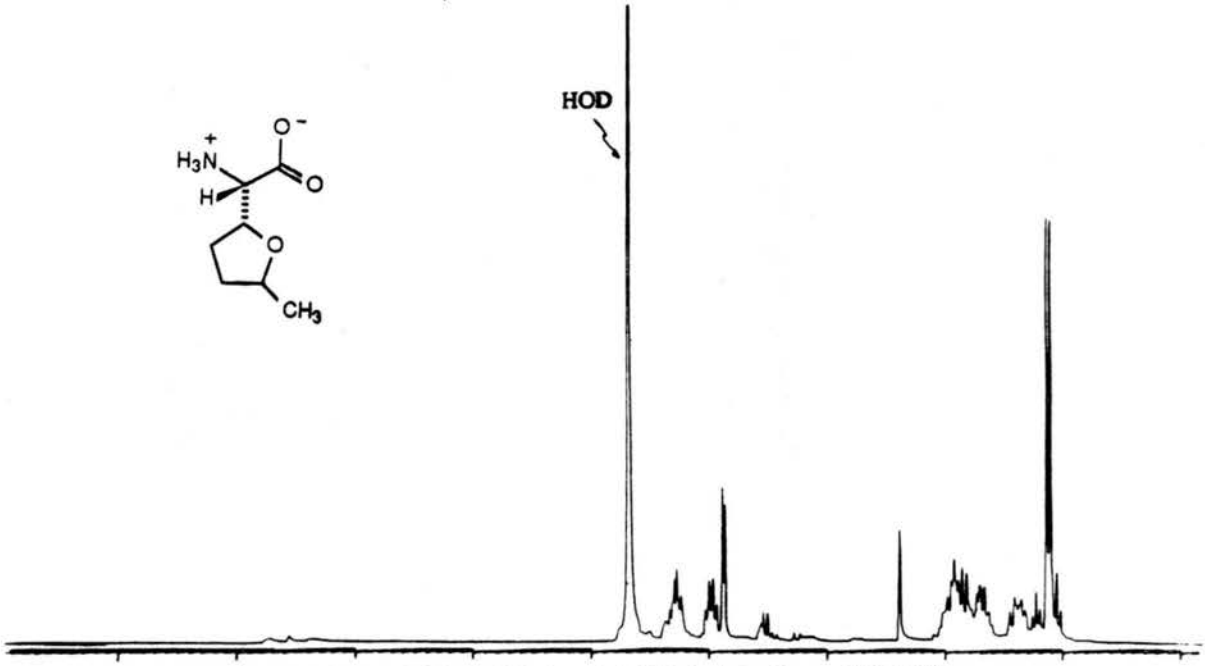
^{1}H NMR (200 MHz) of **150** in DMSO-d_6 at 393°K.



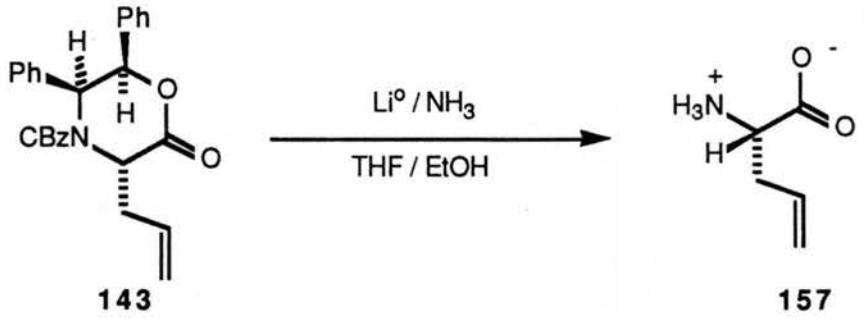
(5'-Methylfuryl)glycine (152) (Dihydrofuranomycin)

To a stirred solution of **150** (100 mg, 0.214 mmol, 1 equiv) in 1:1 THF/EtOH (4 mL) was added $PdCl_2$ (22 mg, 0.064 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 24 h. The mixture was then purged with N_2, filtered through celite, concentrated and triturated with Et_2O leaving 37 mg (110%) **152** as an off-white solid as predominantly one diastereomer.

^1H NMR (major diastereomer) (200 MHz) (D_2O·DCl) δ HOD: 1.12(3H, t, J=6Hz); 1.30-2.05(4H, m); 3.86(1H, d, J=4Hz); 3.97(1H, q, J=4Hz); 4.20-4.35(1H, m). $[\alpha]_D^{25}$ = +4.3 (c = 0.65, 1N HCl).



^1H NMR (200 MHz) of **152** in D_2O at 295°K.

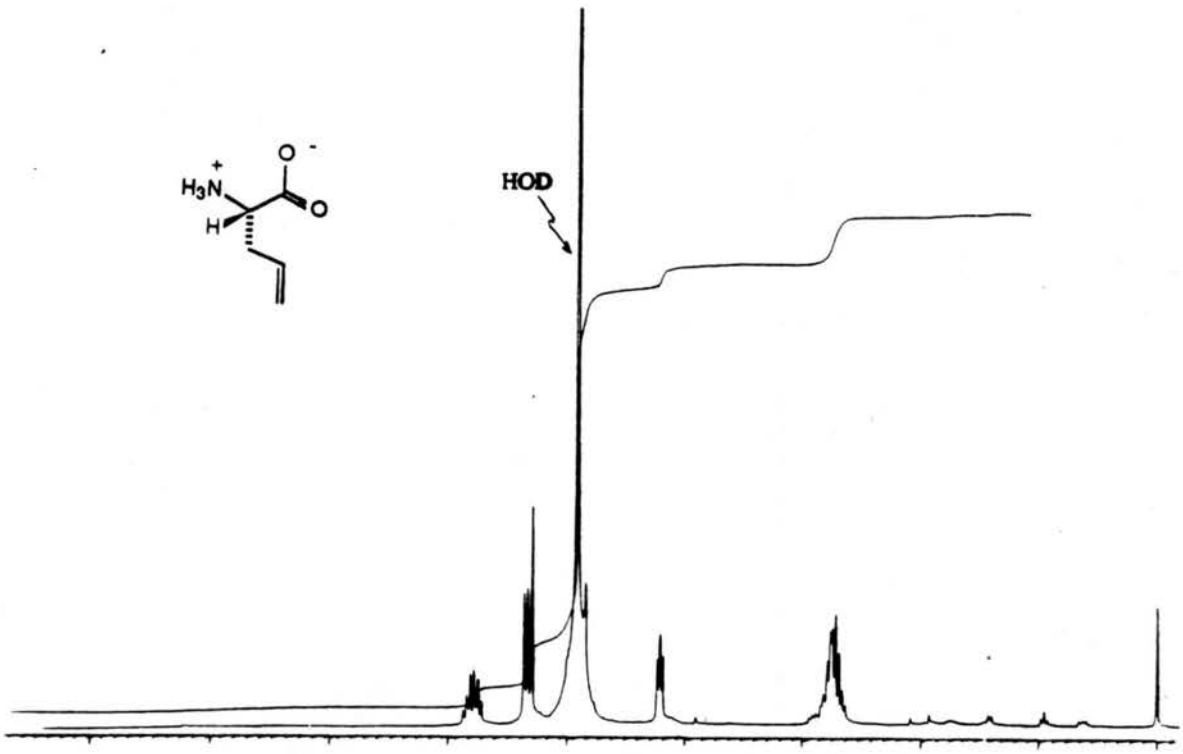


143 157

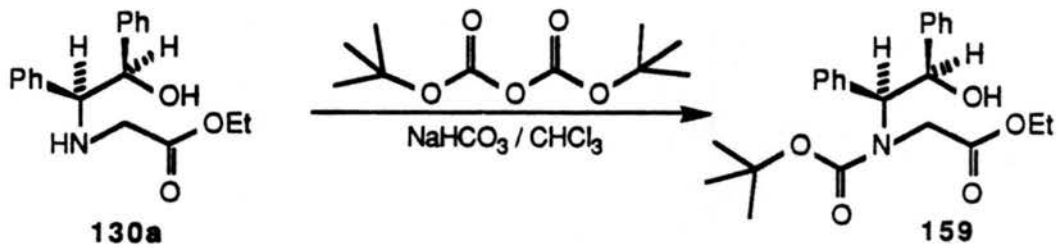
(S)-Allylglycine (157)

To a solution of Li° (49.2 mg, 7.092 mmol, 20 equiv) in NH_3 (25 mL, distilled from Na°) was added a solution of **143** (150 mg, 0.355 mmol, 1 equiv) and EtOH (326 μL) in THF (5 mL) via syringe. After one hour the blue color dissipated and the reaction was quenched with excess NH_4Cl. The ammonia was allowed to evaporate and the residue was diluted with water and extracted with Et_2O. The aqueous layer was loaded onto an ion exchange column (Dowex 50W-X8, H^+ form), washed with water and eluted with 1N NH_4OH. The eluent was concentrated, passed through a Millipore C18 SEPPAK, and concentrated to dryness yielding 36.9 mg (90%) **157** as pure white solid, % ee ≥96 (Figure 24b).

^1H NMR (200 MHz)(D_2O + DCl) δ DSS: 2.64-2.84(2H, m); 4.20(1H, t, J=6.5Hz); 5.29-5.35(2H, m); 5.72-5.87(1H, m). IR(KBr): 3300-2700, 1605, 1585, 1510, 1435, 1405, 1360, 1340, 1305, 1260-1110 cm^{-1}. $[\alpha]_D^{25}$ = -4.4 (c = 0.5, 1N HCl).



^{1}H NMR (200 MHz) of **157** in D_2O/DCl at 295°K.



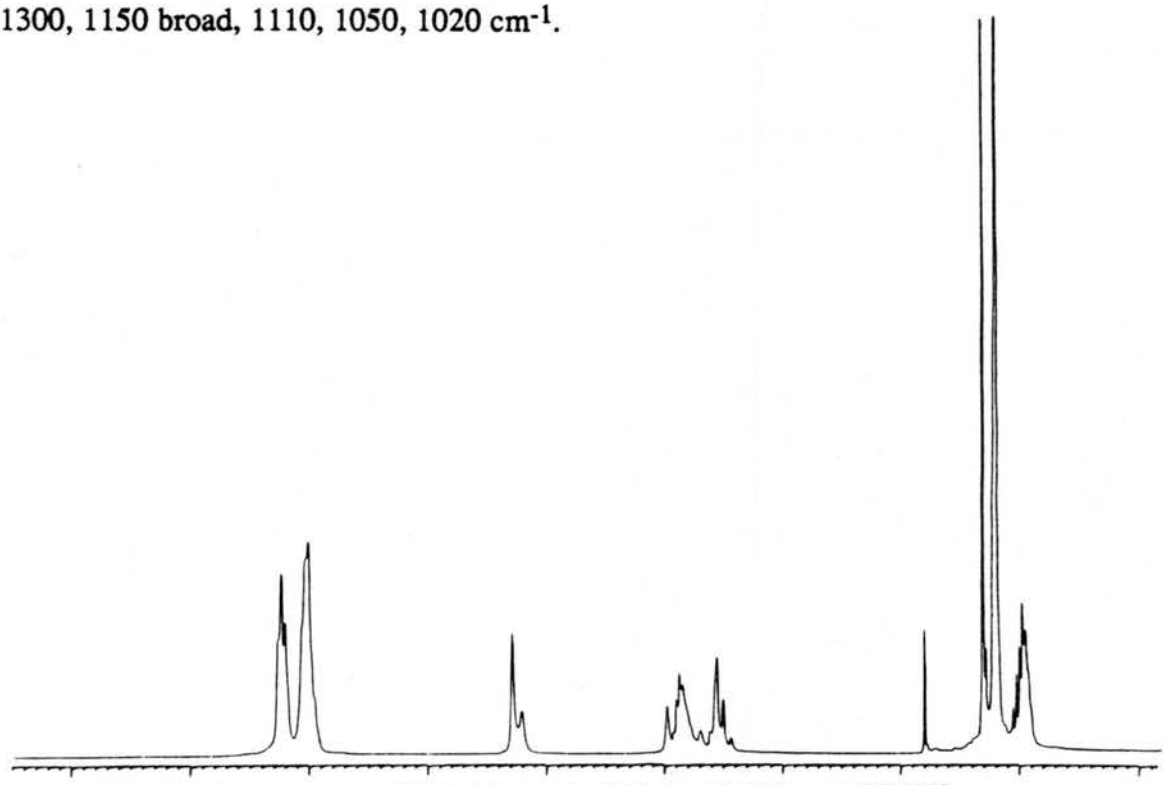
130a **159**

(1'S,2'R)-Ethyl-N-tert-butoxycarbonyl-N-(1',2'-diphenyl-2'-hydroxyethyl)glycinate (159)

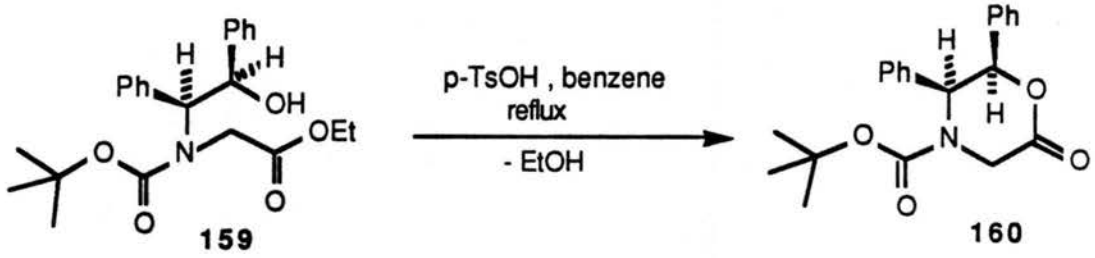
To a solution of 130a (1.50 g, 5.017 mmol, 1 equiv) in $CHCl_3$ (7.5 mL) was added **NaCl (2.05 g, 35.117** mmol, 7 equiv), di-tert-butyldicarbonate (2.3 mL, 10.033 mmol, 2 equiv) followed by addition of a solution of sodium bicarbonate (843 mg, 10.033 mmol, 2 equiv) in water (7.5 mL). The mixture was stirred vigorously and heated to reflux for 4 h. The mxiture was cooled and the aqueous layer was separated and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate,

filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 1.4 g (70%) **159** as a clear oil and 435 mg **130a**. The product was carried on crude.

IR(NaCl, neat): 3440 broad, 2970, 2920, 1800, 1730 broad, 1430, 1380, 1360, 1300, 1150 broad, 1110, 1050, 1020 cm^{-1}.



^1H NMR (270 MHz) of **159** in $CDCl_3$ at 295°K.

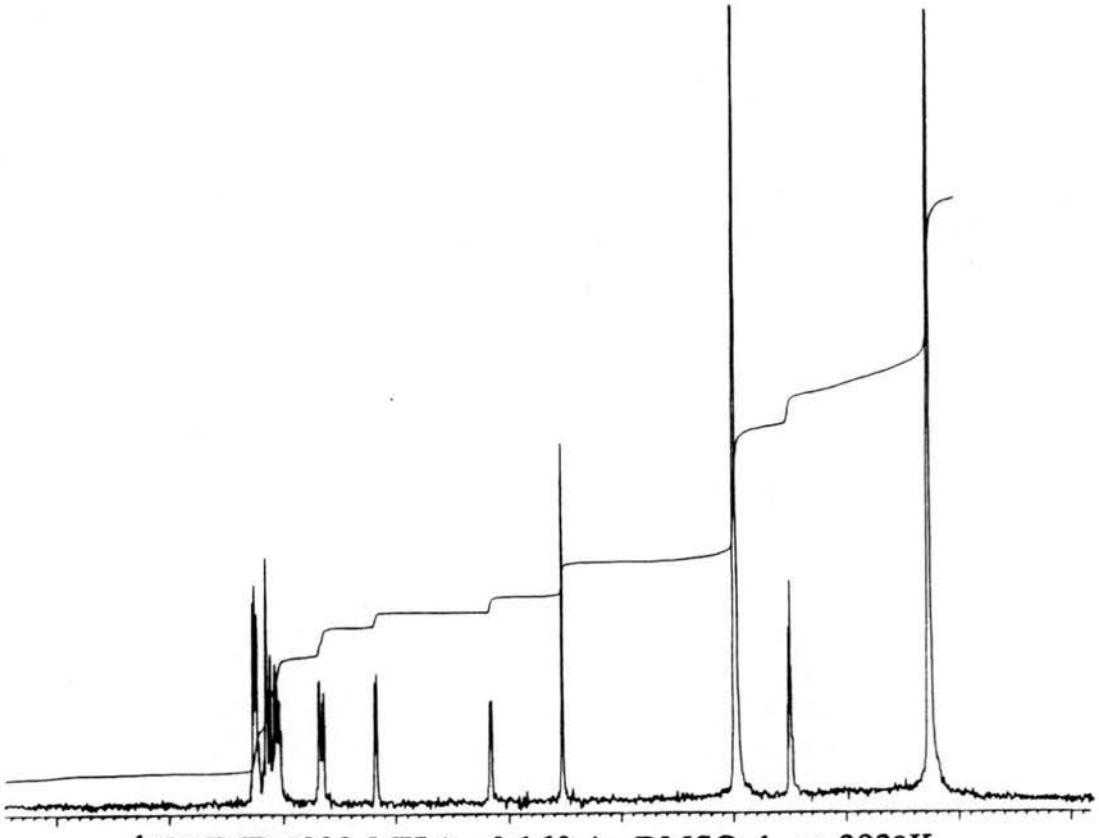


(5S,6R)-4-tert-Butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (160)

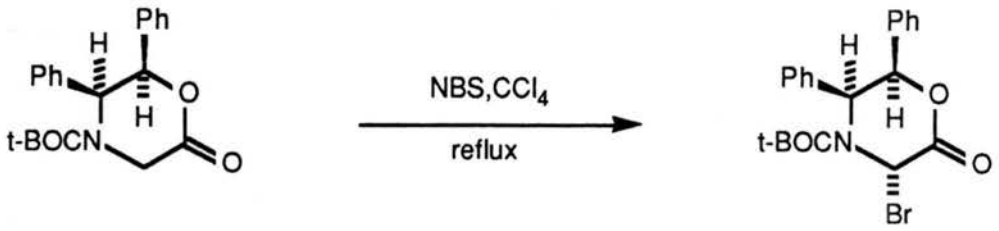
To a stirred solution of **159** (1.754 g, 4.395 mmol, 1 equiv) in benzene (200 mL) was added ρ-toluenesulfonic acid (15 mg, 0.08 mmol, 0.02 equiv). The flask was fitted with an empty Dean-Stark trap and the mixture was brought to reflux. After approximately

100 ml of benzene was collected, hexanes were added and the product was allowed to crystallize yielding 1.02 g (66%) **160** as pure white crystals.

^{1}H NMR (200 MHz) (DMSO-d_6)(393°K) δ DMSO: 1.25(9H, s); 4.52(2H, d, J=1.1Hz); 5.16(1H, d, J=3.0Hz); 6.17(1H, d, J=3.0Hz); 6.63-6.68(2H, m); 7.0-7.3(8H, m). IR(NaCl, CH_2Cl_2): 3050, 2975, 1755, 1690, 1380, 1255, 1150, 1100, 1045 mc^{-1}. Mass spectrum (NH_3)(CI): 370.8(M^+ +18, 2.7%); 353.8(M^+ +1, 0.5%); 251.8(100%). Analysis (recrystallized EtOAc/hexanes) calculated for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.44; N, 3.98, mp 202-203.5°, $[\alpha]_D^{25}$ = -85.3 (c = 1.00, CH_2Cl_2).



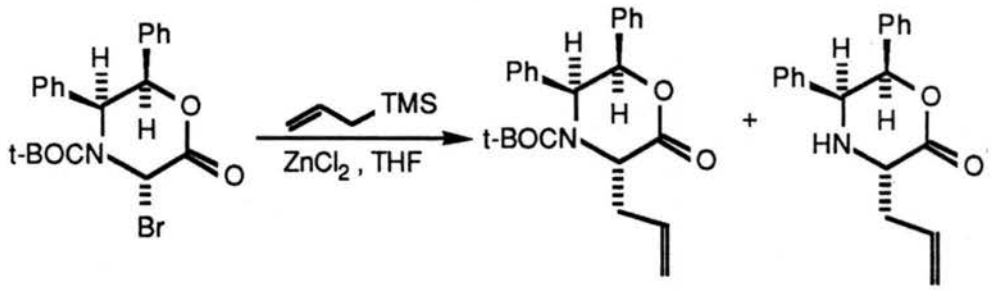
^{1}H NMR (200 MHz) of **160** in DMSO-d_6 at 393°K.



160 161

(3S,5S,6R)-3-Bromo-4-tert-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (161)

To a flask containing **160** (50 mg, 0.142 mmol, 1 equiv) was added CCl_4 (15 mL). The mixture was brought to reflux. When dissolution was complete NBS (28 mg, 0.156 mmol, 1.1 equiv) was added and the mixture was heated to reflux for 1 h, then cooled, filtered to remove succinimide, and concentrated in vacuo to yield **161** as a white solid. The material was used crude.



161 162 163

(3S,5S,6R)-4-tert-butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2-enyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (162) and (3S,5S,6R)-5,6-Diphenyl-3-(1'-prop-2-enyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (163)

To a stirred solution of **161** (153 mg, 0.354 mmol, 1 equiv) in dry THF (4 mL) was added allyltrimethylsilane (225 μL, 1.416 mmol, 4 equiv) followed by addition of $ZnCl_2$ (354 μL, 0.708 mmol, 2 equiv, 2M in THF). After 4 h the mixture was poured into water and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over

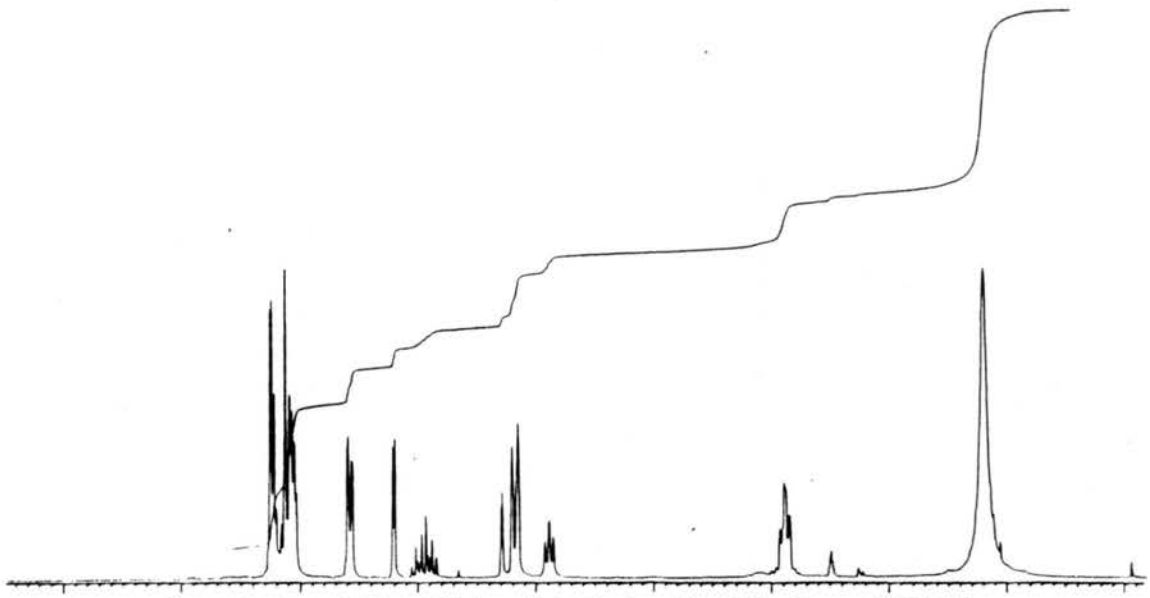
anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 87.6 mg (63%) **162** as a white solid and 15.2 mg (15%) **163** as a clear oil.

162:

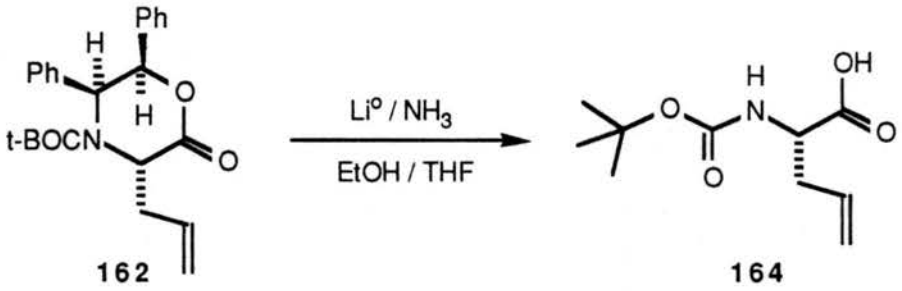
^{1}H NMR (200 MHz) (DMSO-d_6) (393°K) δ DMSO: 1.20(9H, s broad); 2.87(2H, m); 4.88(1H, t, J=7Hz); 5.15-5.29(3H, m); 5.84-6.05(1H, m); 6.20(1H, d, J=3Hz); 6.55(1H, d, J=1.7Hz); 6.59(1H, d, J=1.2Hz); 7.0-7.3(8H, m). IR(NaCl, CH_2Cl_2): 3050, 2970, 2920, 1755, 1690, 1375, 1350, 1260, 1155, 1110 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 411(M^+ +18, 0.5%); 393.9(M^+ +1, 0.5%); 294(100%); 251.9(26%). Analysis (recrystallized Et_2O/hexanes) calculated for $C_{28}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.37;H, 6.85; N, 3.68, mp 177-178°, $[\alpha]_D^{25}$ = -45.8 (c = 1.34, CH_2Cl_2).

163:

^{1}H NMR (200 MHz) ($CDCl_3$) δ $CHCl_3$: 2.05(1H, s broad); 2.84(2H, m); 4.09(1H, dd, J=5.1Hz, J=8.2Hz); 4.74(1H, d, J=3.7Hz); 5.15-5.23(2H, m); 5.71(1H, d, J=3.7Hz); 5.78-5.99(1H, m); 6.92-7.33(10H, m).



^{1}H NMR (200 MHz) of **162** in DMSO-d_6 at 393°K.

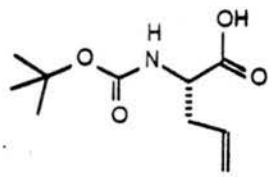


162 164

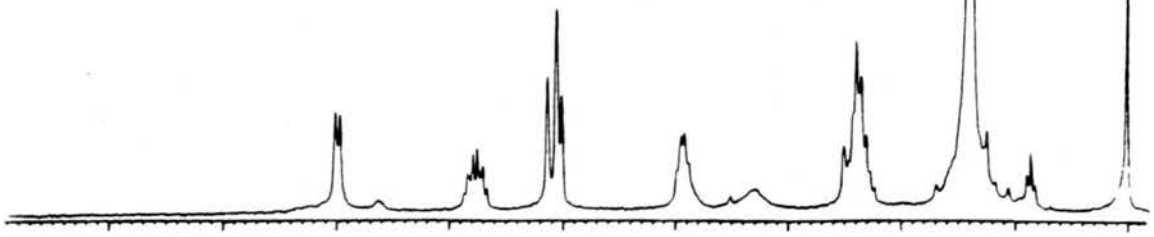
(S)-N-t-butoxycarbonyl Allylglycine (164)

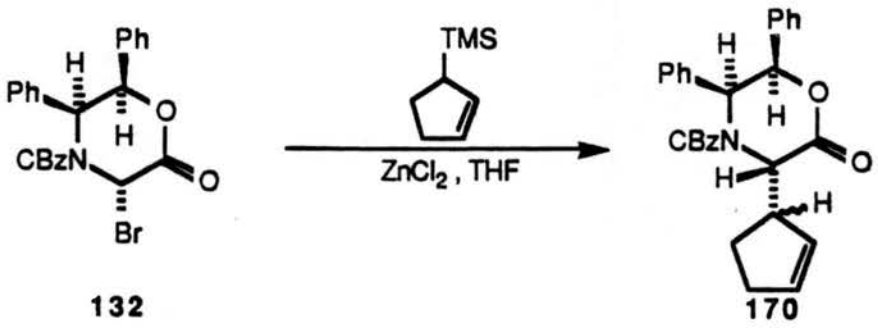
To a stirred solution of Li° (22 mg, 3.23 mmol, 13 equiv) in NH_3 (25 mL) at -33°C was added a solution of **162** (98 mg, 0.25 mmol, 1 equiv) and EtOH (150 μL) in dry THF (5 mL) via syringe. After 15 min the blue color dissipated and the reaction was quenched with NH_4Cl. The mixture was allowed to warm. After the NH_3 evaporated the residue was diluted with water and extracted 2x with Et_2O. The aqueous layer was carefully acidified with 1N HCl to a pH of 3 while stirring with EtOAc. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with 5% MeOH/CH_2Cl_2) to afford 38 mg (71%) **164** as a colorless oil, % ee ≥96.

^1H NMR (200 MHz) (DMSO-d_6) (310°K) δ TMS: 1.37(9H, s); 2.2-2.5(2H, m); 3.8-4.0(1H, m); 5.0-5.2(2H, m); 5.6-5.9(1H, m); 7.0(1H, d, J=8Hz); 11.65(1H, broad). IR(NaCl, neat): 3430, 3050, 2980, 1715, 1500, 1370, 1265, 1155 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 232.9(M^+ +18, 1.8%); 215.9(M^+ +1, 2.1%); 214.9(M^+, 0.3%); 116.0(62.9%), $[\alpha]_D^{25}$ = -3.8 (c = 1.5, CH_2Cl_2).



^{1}H NMR (200 MHz) of **164** in DMSO-d_6 at 310°K.





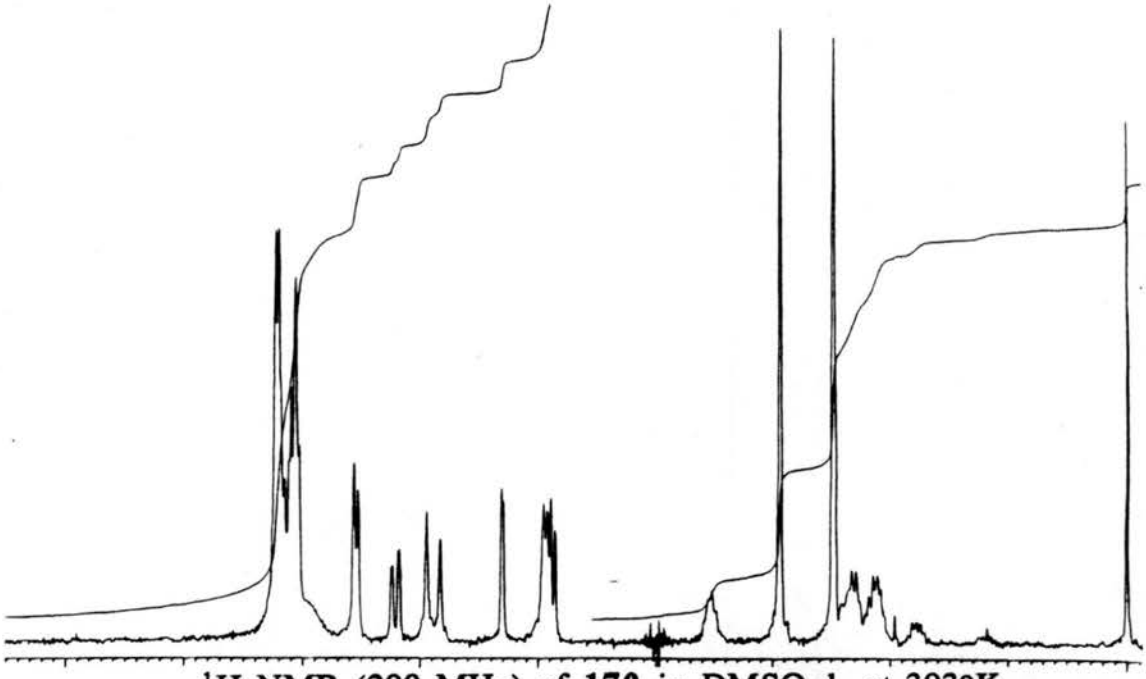
132 **170**

(3S,5S,6R)-4-Benzyloxycarbonyl-3-(2'-cyclopentenyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (170)

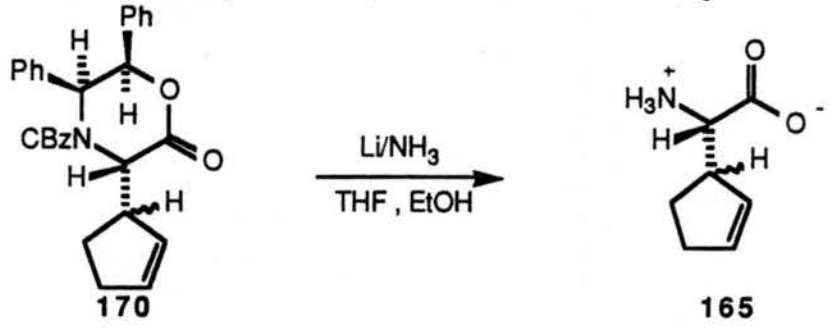
To a stirred solution of **132** (301 mg, 0.646 mmol, 1 equiv) in dry THF (5 mL) was added 3-(trimethylsilyl)cyclopentene (460 μL, 2.584 mmol, 4 equiv) followed by addition of $ZnCl_2$ (646 μL, 1.292 mmol, 2 equiv, 2M solution in THF). The mixture was stirred for 15 h, poured into water and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 240 mg (82%) **170 as a white solid,** as approximately a 1:1 mixture of diastereomers.

^{1}H NMR (200 MHz) (393°K)(DMSO-d_6) δ $(CH_3)_4Si$: 2.05-2.45(4H, m); 3.55(1H, m); 4.8-5.0(2H, m); 5.32(1H, d, J=3Hz); 5.8-6.0(2H, m); 6.15-6.25(1H, as 2d, J=3Hz); 6.5-6.6(2H, m); 7.0-7.4(14H, m). IR(NaCl, CH_2Cl_2): 3030, 1750, 1700, 1450, 1400, 1260, 110 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 471(M^+ +18, 11%), 453.5(M^+, 73%); 251.9(88%). Analysis (recrystallized EtOAc/hexanes) calculated for

$C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09. Found: C, 76.65; H, 6.07; N, 3.09. mp 188.5-186, $[\alpha]_D^{25}$ = -25.8 (c = 0.94, CH_2Cl_2).



^{1}H NMR (200 MHz) of **170** in DMSO-d_6 at 393°K.



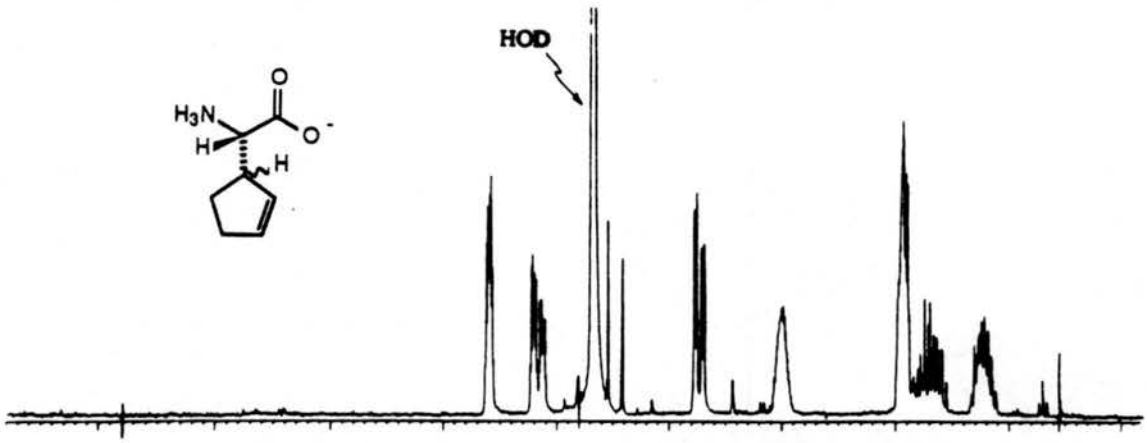
170 **165**

(2'-Cyclopentenyl)glycine (165)

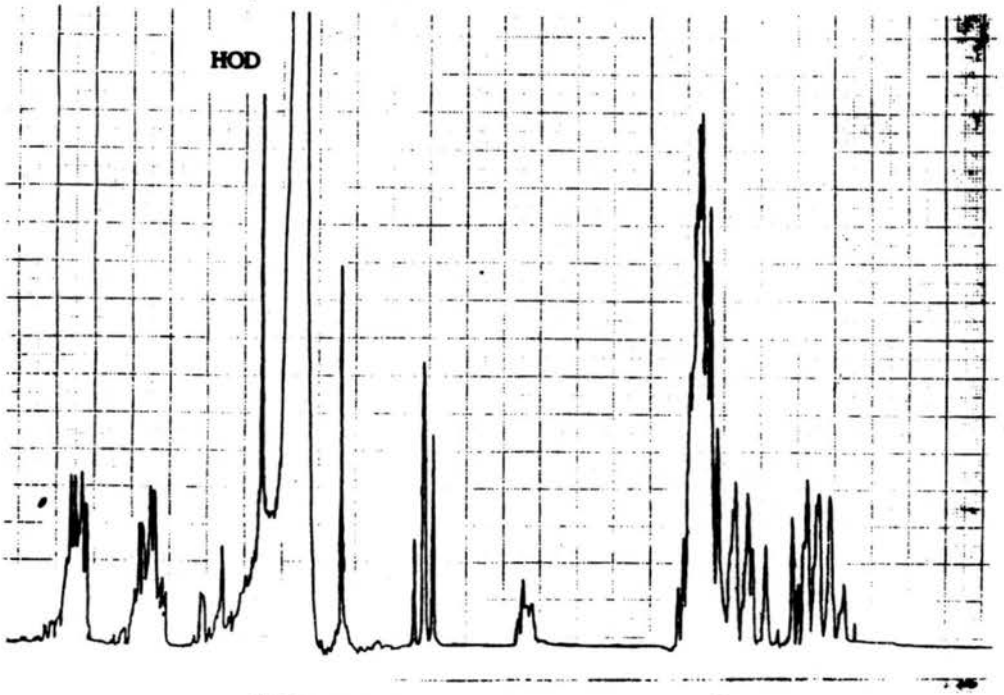
To a solution of Li° (52 mg, 7.549 mmol, 20 equiv) in NH_3 (25 mL, distilled from Na°) was added a solution of **170** (171 mg, 0.377 mmol, 1 equiv) and EtOH (347 μL) in THF (5 mL) via syringe. After 1 h the blue mixture was quenched with excess NH_4Cl and the ammonia was allowed to evaporate. The residue was diluted with water and extracted with Et_2O. The aqueous layer was loaded onto an ion exchange resin (Dowex 50W-X8, H^+ form), washed with water, and eluted with 1N NH_4OH. The eluent was concentrated,

passed through a Millipore C18 SEPPAK, and concentrated to dryness yielding 50 mg (94%) **165** as a white solid, as a 1:1 mixture of diastereomers.

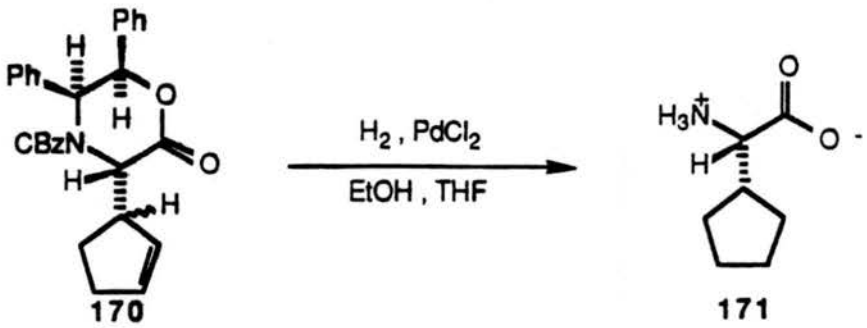
^{1}H NMR (200 MHz) (D_2O + DCl) δ DSS: 1.52-1.79(1H, m); 1.83-21.4(1H, m); 2.29-2.38(2H, m); 3.13(1H, broad s); 3.30-3.41(1H, m); 5.56-5.85(1H, m); 5.89-5.92(1H, m). IR(KBr): 3600-3300, 3050, 2940, 1610, 1585, 1510, 1420, 1340, 1415, 1140, 1120 cm^{-1}. $[\alpha]_D^{25}$ = +1.4 (c = 0.56, 1N HCl).



^{1}H NMR (200 MHz) of **165** in D_2O/DCl at 295°K.



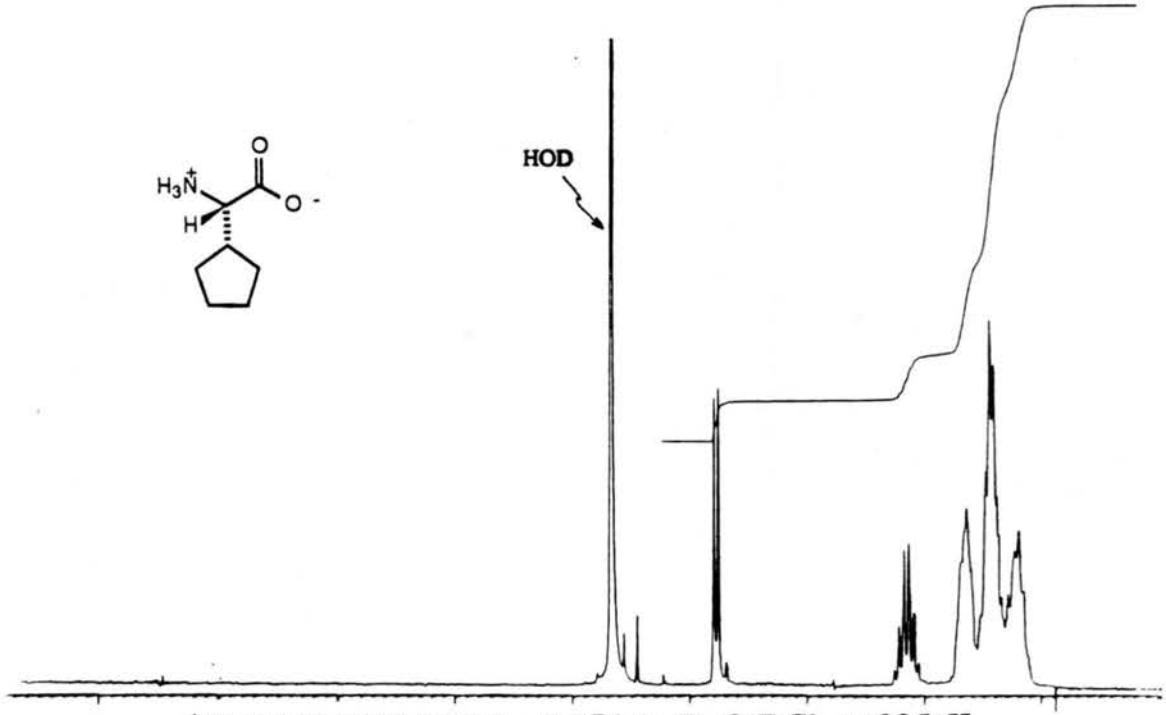
^{1}H NMR (90 MHz) Authentic **165**[60]



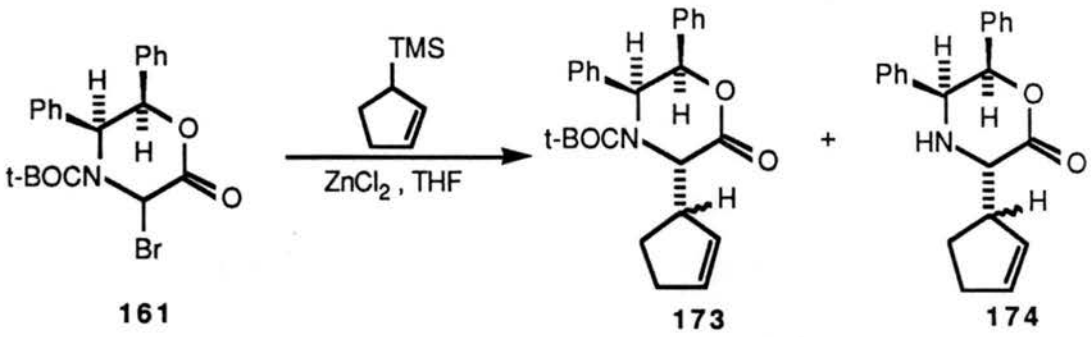
S-Cyclopentylglycine (171)

To a solution of **170** (150 mg, 0.33 mmol, 1 equiv) in 1:1 EtOH/THF (6 mL) was added $PdCl_2$ (33 mg, 0.1 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 28 h, then purged with N_2, filtered through celite to remove the catalyst, concentrated in vacuo, and triturated with Et_2O several times to afford 56 mg (118%) **171** as a pure white solid, % ee ≥96 (Figure 25b).

^{1}H NMR (200 MHz)(D_2O + DCl) δ DSS: 1.3-1.9(8H, m); 2.36(1H, q, J=9Hz); 3.99(1H, d, J=7.4Hz). IR(KBr): 3600-3300, 2850, 2760, 1605, 1585, 1510, 1420, 1395, 1340, 1130 cm^{-1}. $[\alpha]_D^{25}$ = +11.6 (c = 0.49, 1N HCl).



^{1}H NMR (200 MHz) of **171** in D_2O/DCl at 295°K.



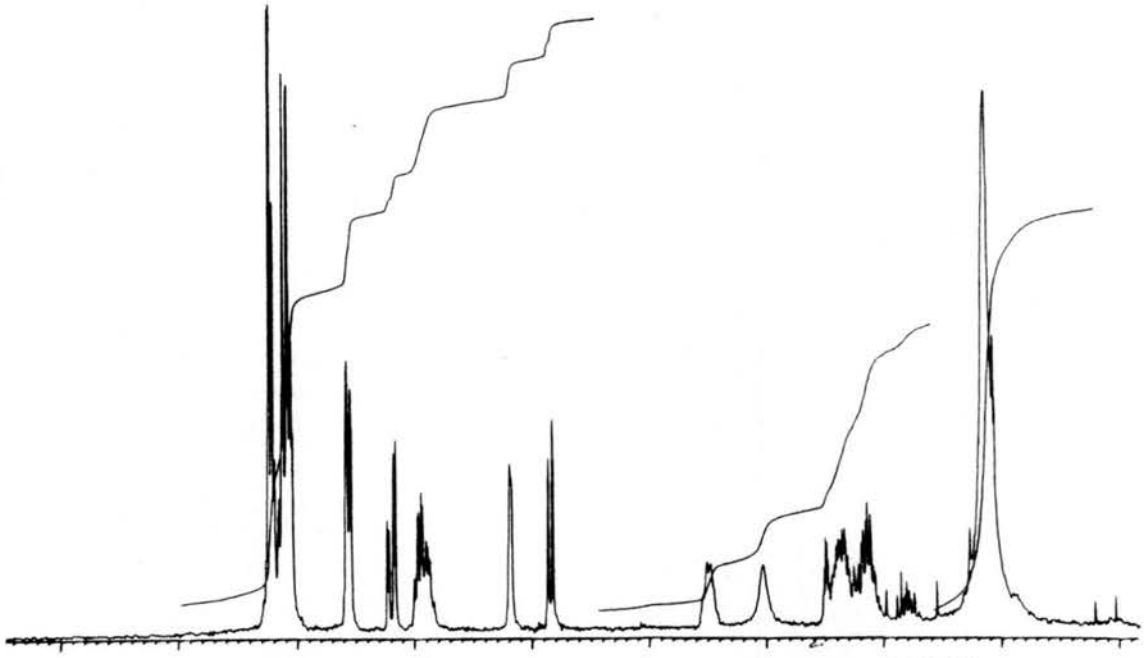
161 **173** **174**

(3S,5S,6R)-4-tert-butoxycarbonyl-3-(2'-cyclopentenyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (173) and (5S,6R)-3-(2'-cyclopentenyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (174)

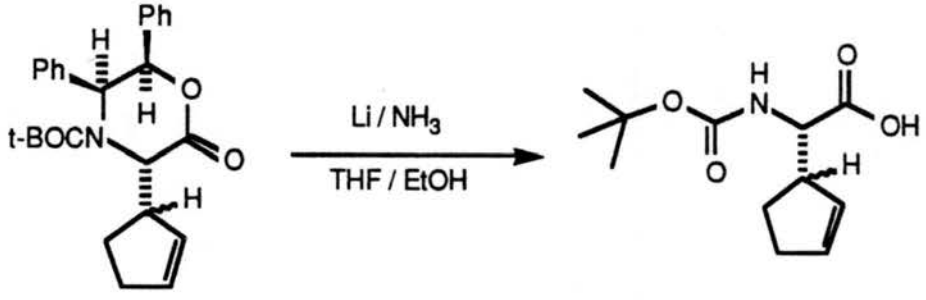
To a stirred solution of **161** (153 mg, 0.3541 mmol, 1 equiv) in dry THF (4 mL) was added 3-(trimethylsilyl)cyclopentene (250 μL, 1.416 mmol, 4 equiv) followed by addition of $ZnCl_2$ (350 μL, 0.708 mmol, 2 equiv, 2M in THF). After 16 h the mixture was poured into water and extracted 4x with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 84.9 mg (58.7%) **173** as a white solid as approximately a 2:1 mixture of diastereomers and 20 mg (18%) **174** as a clear oil.

173:

^1H NMR (200 MHz) (DMSO-d_6)(393°K) δ DMSO: 1.13(9H, broad s); 2.05-2.45(4H, m); 3.49(1H, m); 4.84(1H, as 2 singlets); 5.19(1H, s); 5.8-6.0(2H, m); 6.22(1H, as 2 doublets, J=3Hz); 6.54(1H, s); 6.57(1H, s); 7.0-7.3(8H, m). IR(NaCl, CH_2Cl_2): 3050, 2980, 1760, 1700, 1455, 1380, 1370, 1355, 1340, 1265, 1160, 1115 cm^{-1}. Analysis (recrystallized from EtOAc/hexanes) calculated for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.56; H, 7.08; H, 3.30, mp 183-184.5°.



^{1}H NMR (200 MHz) of **173** in DMSO-d_6 at 393°K.



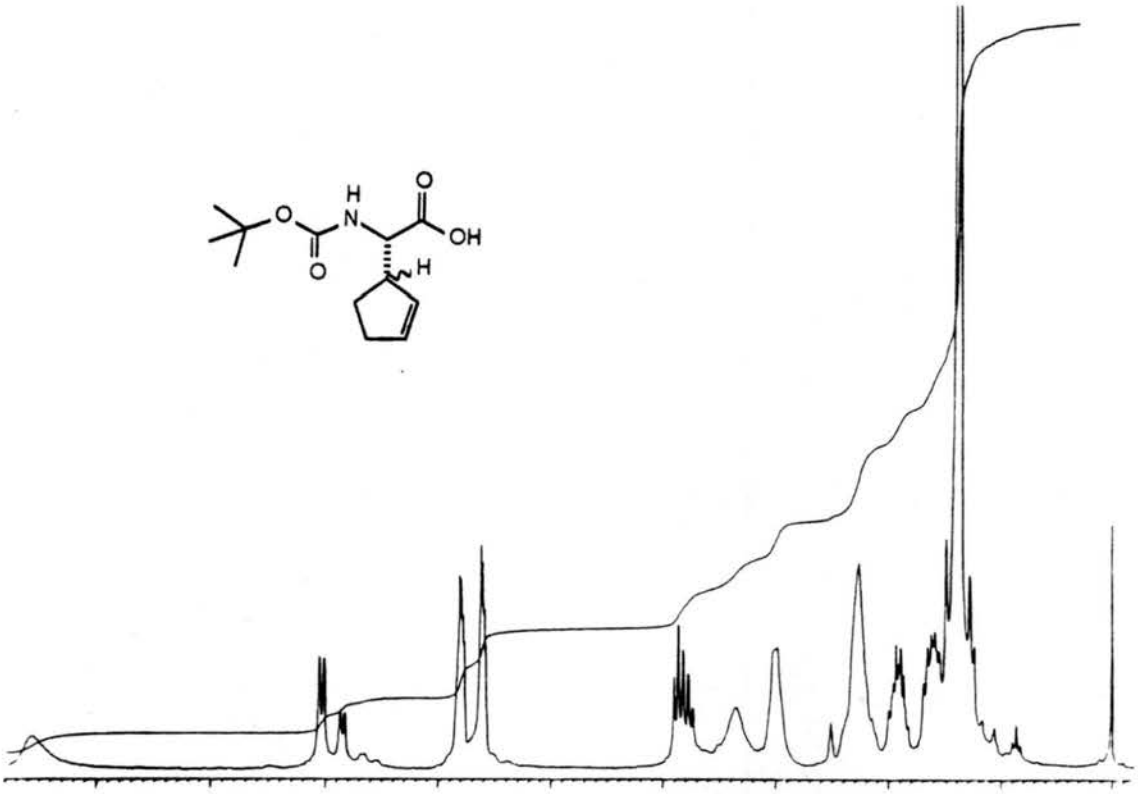
173 **175**

(2S,2'S) and (2S,3'R)-N-tert-butoxycarbonylcyclopentenylglycine (175)

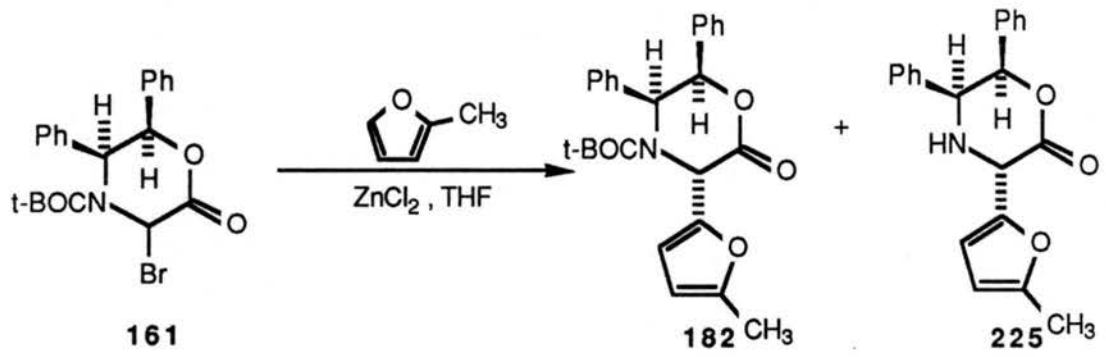
To a stirred solution of Li° (18 mg, 2.67 mmol, 13 equiv) in NH_3 (25 mL, distilled from Na°) at -33°C was added a solution of **173** (86 mg, 0.21 mmol, 1 equiv) and EtOH (125 µL) in dry THF (5 mL) via syringe. After 25 min the blue color dissipated and the reaction was quenched with excess NH_4Cl. The mixture was allowed to warm. After the NH_3 evaporated the residue was diluted with water and extracted 2x with Et_2O. The aqueous layer was carefully acidified to a pH of 3 with 1N HCl while stirring with EtOAc. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, concentrated and

passed over a silica gel plug (eluted with 10% MeOH/CH_2Cl_2) to afford 38 mg (77%) **175** as a slightly yellow oil as approximately a 2:1 mixture of diastereomers.

^{1}H NMR (200 MHz) (DMSO-d_6) (310°K) δ TMS: 1.37(9H, s); 1.54-1.68(1H, m); 1.82-1.99(1H, m); 2.25(2H, broad s); 2.93-3.0(1H, broad m); 3.73-3.89(1H as 2 triplets: 3.77, J=7.9Hz; 3.85, J=7.5Hz); 5.5-5.65(1H, m); 5.76-5.83(1H, m); 6.84-7.03(1H, as 2 doublets: 6.84, J=8Hz; 7.03, J=8Hz); 9.4-9.7(1H, broad s). IR(NaCl, neat): 3440, 3060, 2980, 2930, 1710, 1500, 1265, 1165 cm^{-1}. Mass spectrum (NH_4)(CI): m/e = 276(M^+ +35, 0.2%); 258(M^+ +18, 0.2%); 242(M^+ +1, 0.5%); 141.9(12.7%). $[\alpha]_D^{25}$ = +10.6 (c = 0.31, CH_2Cl_2).



^{1}H NMR (200 MHz) of **175** in DMSO-d_6 at 310°K.

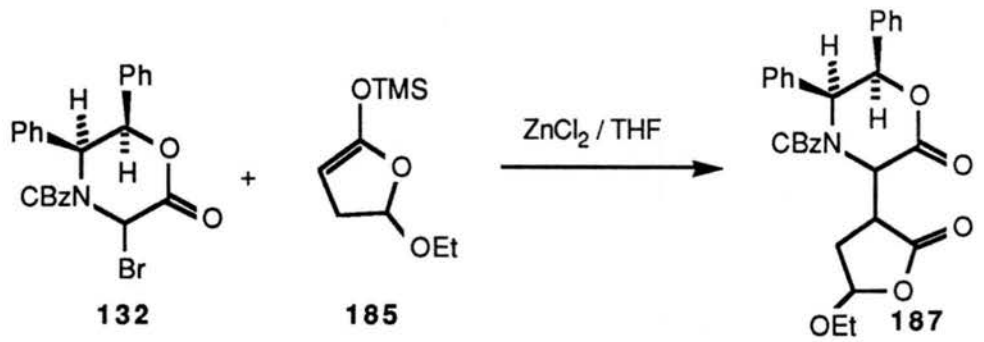


(5S,6R)-4-t-Butoxycarbonyl-5,6-diphenyl-3-(2'-(5'-methylfuryl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one (182)

To a stirred solution of **161** (122 mg, 0.283 mmol, 1 equiv) in THF (2 mL) was added 2-methylfuran (425 μL, 4.25 mmol, 15 equiv) via syringe followed by addition of $ZnCl_2$ (283 μL, 0.567 mmol, 2 equiv, 2.0 M in THF). After 3 h the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial chromatrography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 35 mg (28%) **182** and 28 mg (30%) **225**.

182

^1H NMR (270 MHz) ($CDCl_3$) δ (CH_4)Si: 1.09(5H, s); 1.38(4H, s); 2.3(3H, s); 5.1-5.4(1H, m); 6.0-6.5(4H, m); 6.6-6.75(2H, m); 6.95-7.0(2H, m); 7.05-7.3(8H, m). Mass spectrum (NH_3)(CI): m/e = 451(M^+ +18, 4.0%); 434(M^+ +1, 6.1%); 334(18.9%); 251.8(7.5).

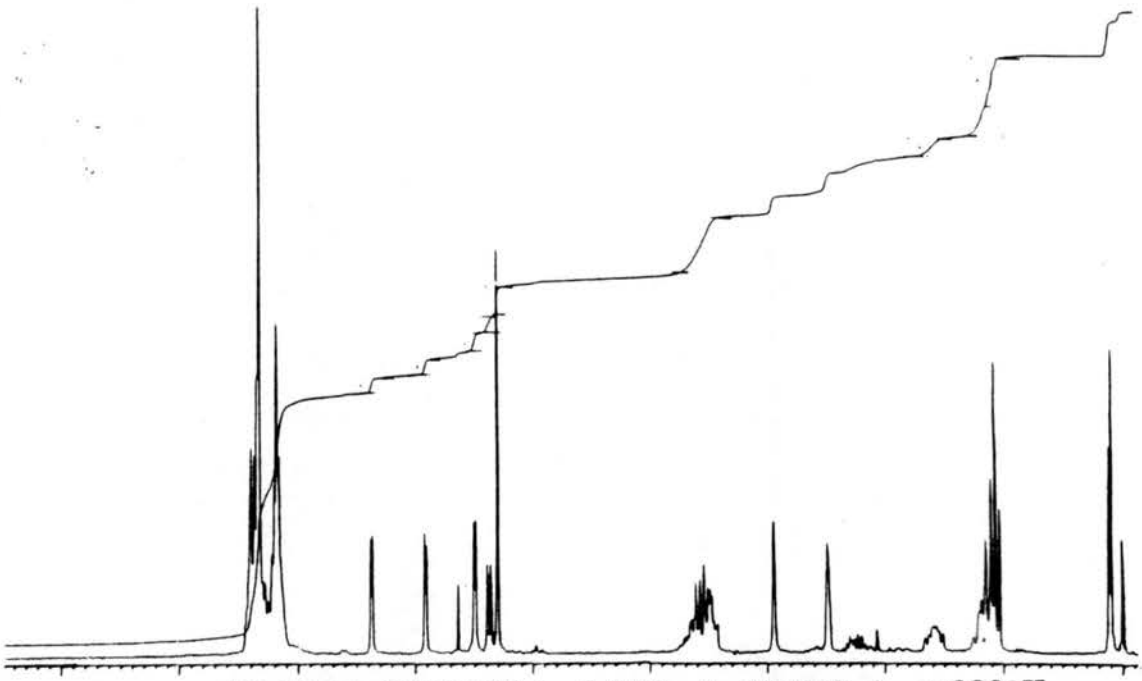


(5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(3'-(5'-ethoxy-γ-butyrolactonyl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one (187)

To a stirred solution of **132** (300 mg, 0.646 mmol, 1 equiv) in THF (5 mL) was added the trimethylsilyl ketene acetal of γ-ethoxybutyrolactone (290 μL, 1.938 mmol, 3 equiv) via syringe followed by addition of $ZnCl_2$ (400 μL, 0.323 mmol, 0.5 equiv, 0.8M in THF). After 50 min the reaction mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated. The procedure was repeated and the two product mixtures were separated by flash column chromatography on silica gel (eluted with 1:9 EtOAc/hexane) to afford 173 mg **187a**, 153 mg **187b**, and 89 mg **187c** (mixture of diastereomers) 62% overall.

187a

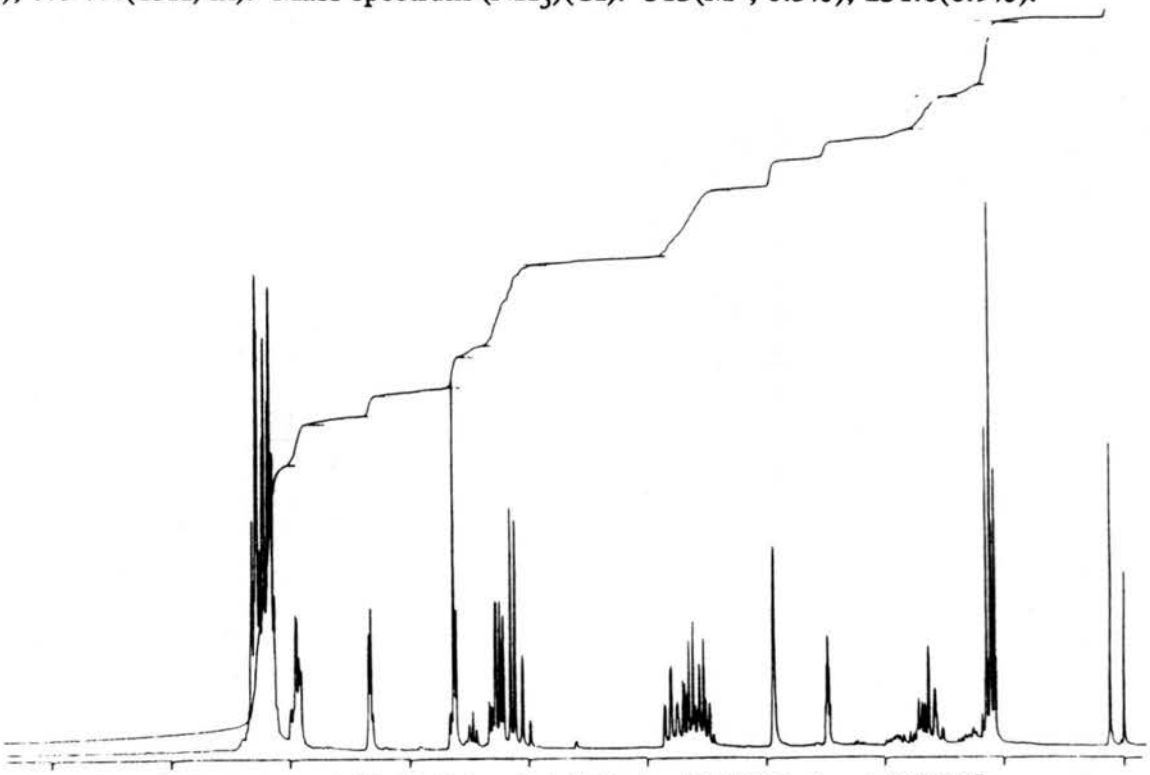
^1H NMR (200 MHz) (DMSO-d_6)(393°K) δ $(CH_3)_4Si$: 1.0-1.25(4H, m); 1.5-1.7(1H, m); 3.4-3.7(3H, m); 5.3(2H, s); 5.37(1H, d, J=5.85Hz); 5.49(1H, d, J=3Hz); 5.90(1H, d, J=3Hz); 6.36(1H, d, J=3Hz); 7.1-7.45(15H, m). IR(NaCl, neat): 3055, 2980, 2920, 1775, 1745, 1700, 1495, 1450, 1400 cm^{-1}. Mass spectrum (NH_3)(CI): 515(M^+, 0.2%); 251.8(0.5%).



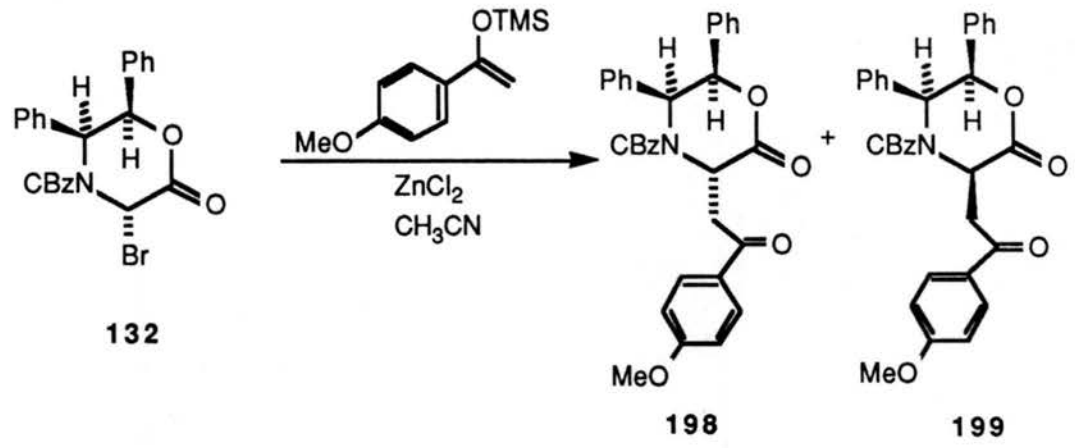
^{1}H NMR (200 MHz) of **187a** in DMSO-d_6 at 393°K.

187b

^{1}H NMR (200 MHz) (DMSO-d_6)(393°K) δ $(CH_3)_4Si$: 1.04-1.14(3H, m); 1.51-1.78(2H, m); 3.47-3.85(3H, m); 4.98-5.33(4H, m); 5.63-1H, m); 6.32(1H, m); 6.9(2H, m); 7.0-7.4(13H, m). Mass spectrum (NH_3)(CI): 515(M^+, 0.3%); 251.8(0.9%).



^{1}H NMR (200 MHz) of **187b** in DMSO-d_6 at 393°K.



132 **198** **199**

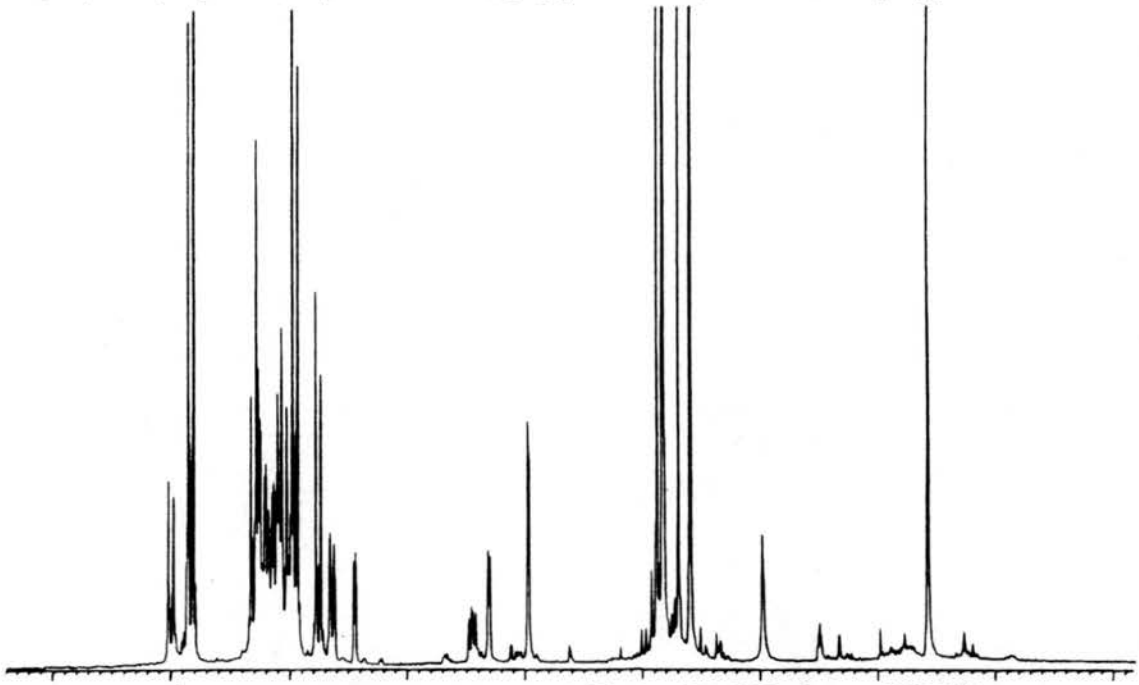
(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-[1'-(2'-(4"-methoxy)phenylethan-2'-onyl)]-2,3,5,6-tetrahydro-1,4-oxazin-2-one (198) and (3R,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-[1'-(2'-(4"-methoxy)phenylethan-2'-onyl)]-2,3,5,6-tetrahydro-1,4-oxazin-2-one (199)

To a stirred suspension of **132** (234 mg, 0.50 mmol, 1 equiv) in dry CH_3CN (10 mL) was added $ZnCl_2$ (600 μL, 0.45 mmol, 0.9 equiv, 0.76M in THF) followed by addition of the trimethylsilyl enol ether of 4-methoxy acetophenone (525 μL, 2.50 mmol, 5 equiv). After 4 h the solution was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 194 mg (72%) **198**, **199** as a 3:1 mixture of diastereomers. The product mixture was recrystallized 2x giving 80 mg pure **198**.

198

^1H NMR (200 MHz) (DMSO-d_6)(393°K) δ DMSO: 3.77(1H, dd, J_{vic}=4.5Hz, J_{gem}=16.5Hz); 3.87(3H, s); 3.94(1H, dd, J_{vic}=6.9Hz, J_{gem}=16.5Hz); 4.96(2H, s); 5.30(1H, d, J=3Hz); 5.44(1H, dd, J_{vic}=4.5Hz, J_{vic}=6.9Hz); 6.43(1H, d, J=3Hz); 6.61(1H, s); 6.64(1H, s); 6.9-7.4(15H, m); 8.0(2H, d). IR(KBr): 1750, 1710(s), 1695, 1675, 1600, 1395, 1345, 1290, 1275, 1265, 1110 cm^{-1}. Analysis (recrystallized from

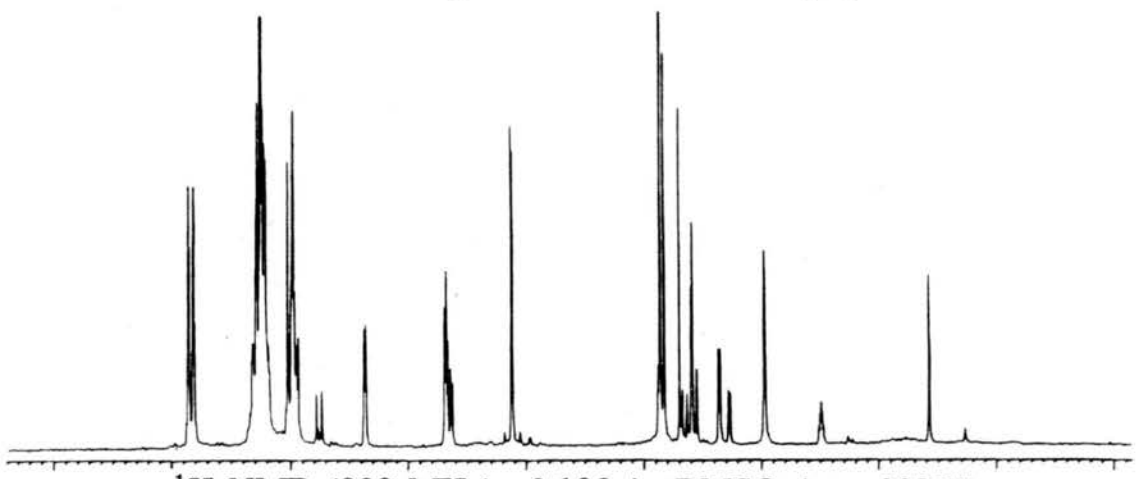
EtOAc/hexanes) calculated for $C_{33}H_{29}NO_6$: C, 74.00; H, 5.46; N, 2.61. Found: C, 74.13; H, 5.57; N, 2.48; mp 178-181°C, $[\alpha]_D^{25}$ = -2.3 (c = 1.12, CH_2Cl_2).



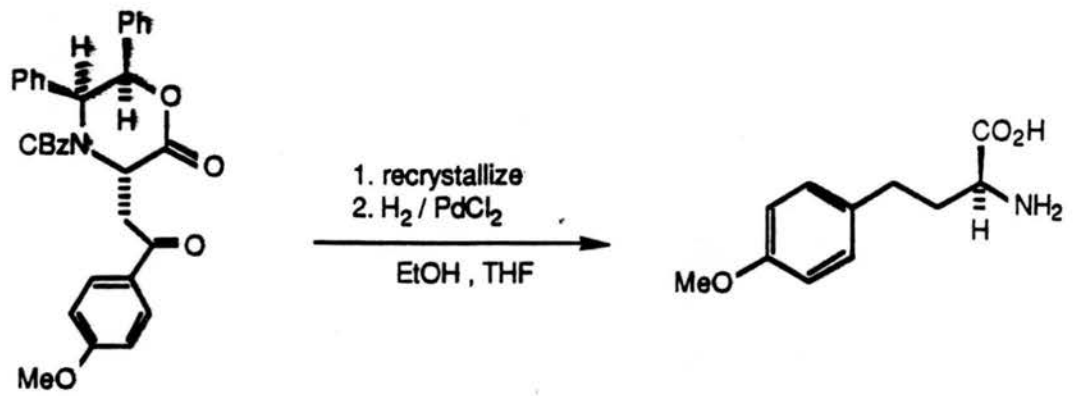
^{1}H NMR (200 MHz) of **198** in DMSO-d_6 at 393°K.

199

^{1}H NMR (200 MHz) (DMSO-d_6)(393°K) δ DMSO: 3.30(1H, dd, J_{vic}=3Hz, J_{gem}=17Hz); 3.61(1H, dd, J_{vic}=7.7Hz, J_{gem}=17Hz); 3.86(3H, s); 5.12(2H, s); 5.65(1H, dd, J_{vic}=7.7Hz, J_{vic}=3Hz); 5.68(1H, d, J=3Hz); 6.36(1H, d, J=3Hz); 6.9-7.9(19H, m). IR(NaCl, CH_2Cl_2): 1750, 1700, 1675, 1595, cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 534.8(M^+, 0.2%); 387.3(0.8%); $[\alpha]_D^{25}$ = +27.9 (c = 1.02, CH_2Cl_2).



^{1}H NMR (200 MHz) of **199** in DMSO-d_6 at 393°K.

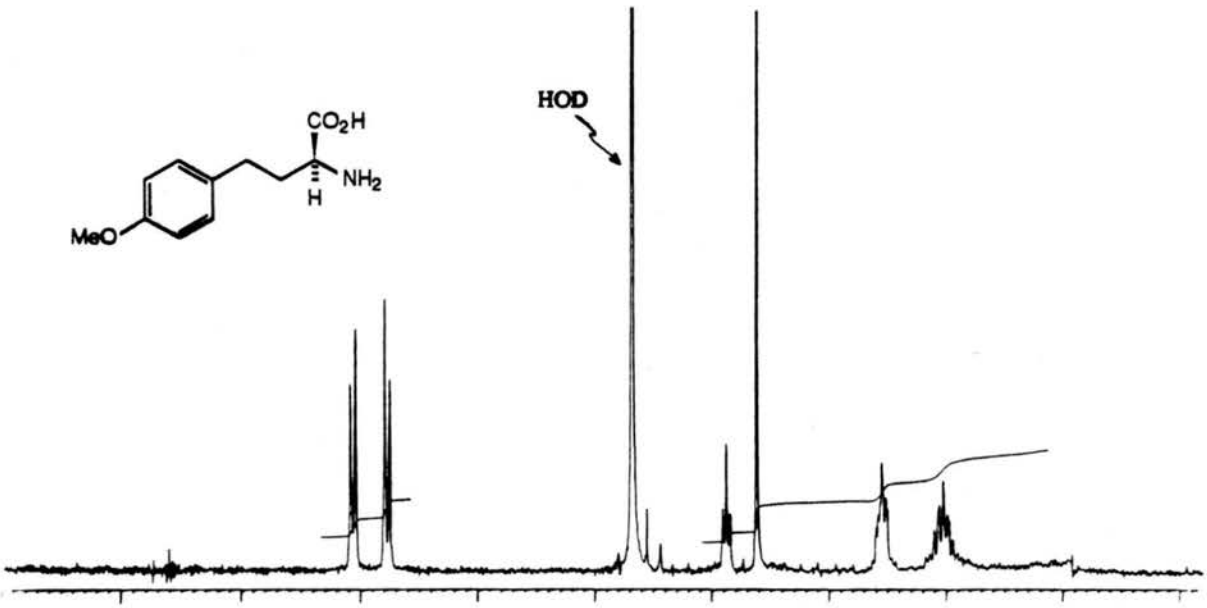


198 191

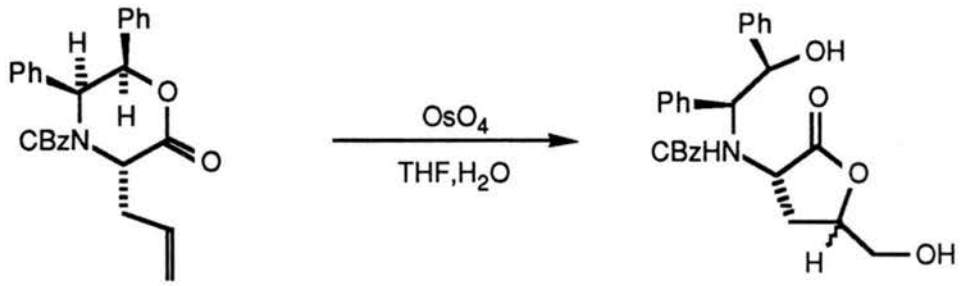
(S)-4'-Methoxyhomophenylalanine (191)

To a stirred solution of **198** (100 mg, 0.18 mmol, 1 equiv) in THF (3 mL) and EtOH (3 mL) was added $PdCl_2$ (19 mg, 0.05 mmol, 0.3 equiv). The mixture was hydrogenated for 24 h at 40 psi H_2. The reaction mixture was then purged with N_2, filtered through celite, concentrated and triturated several times with Et_2O leaving 48 mg (122%) **191** as a pure white solid, % ee ≥98 (Figure 26b).

^1H NMR (200 MHz)(D_2O + DCl) δ HOD: 1.9-2.1(2H, m); 2.4-2.6(2H, m); 3.61(3H, s); 3.87(1H, t, J=6Hz); 6.71(2H, d, J=8.6Hz); 7.06(2H, d, J=8.6Hz). $[\alpha]_D^{25}$ = +34.6 (c = 0.5, 1N HCl).



^1H NMR (200 MHz) of **191** in D_2O/DCl at 295°K.



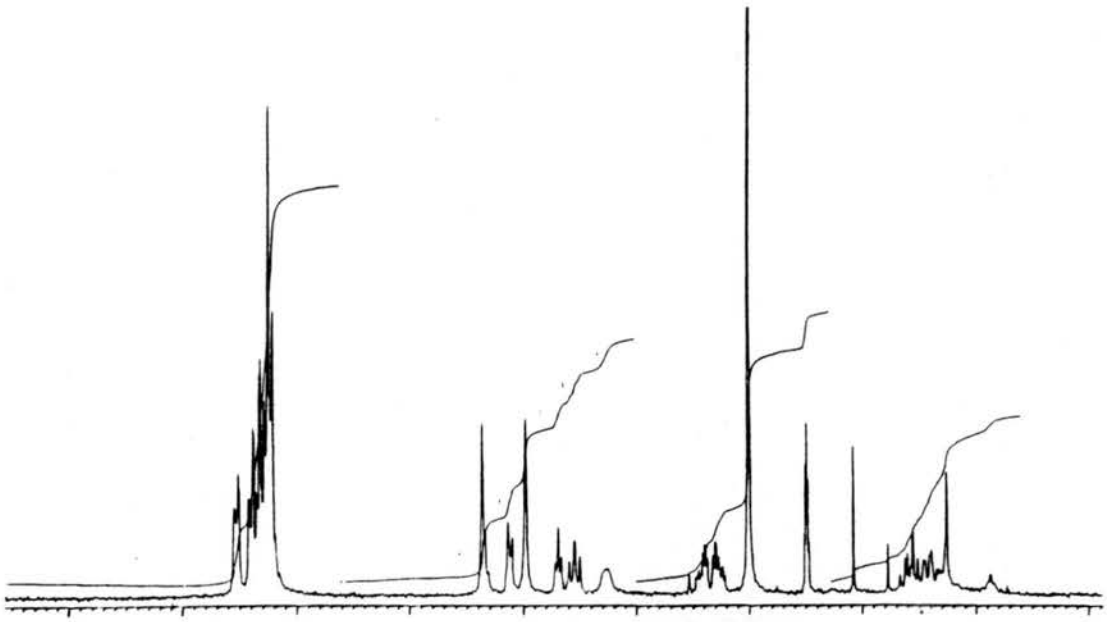
143 **207**

(2S,4R,1'S,2'R)-2-[(N-benzyloxycarbonyl-N-(1',2'-diphenyl-2'-hydroxyethyl))amino]-4-hydroxymethyl-4-hydroxybutyric acid-γ-lactone (207a) and (2S,4S,1'S,2'R)-2-[(N-benzyloxycarbonyl-N-(1',2'-diphenyl-2'-hydroxyethyl))amino]-4-hydroxymethyl-4-hydroxybutyric acid-γ-lactone (207b)

To a stirred solution of **143** (60.4 mg, 0.14 mmol, 1 equiv) in THF (2 mL) was added OsO_4 (910 μL, 0.14 mmol, 1 equiv, 4% solution in water). After stirring the dark brown mixture, a solution of $NaHSO_3$ and pyridine in water (175 mg : 5.5mL : 8.5mL) was added and the mixture was stirred an additional 2.5 h. The mixture was then thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, concentrated, and separated by radial chromatography on silica gel (eluted with 2.5% CH_3OH/CH_2Cl_2) to afford 52 mg (78%) **207** as a 1:1 mixture of diastereomers.

207a

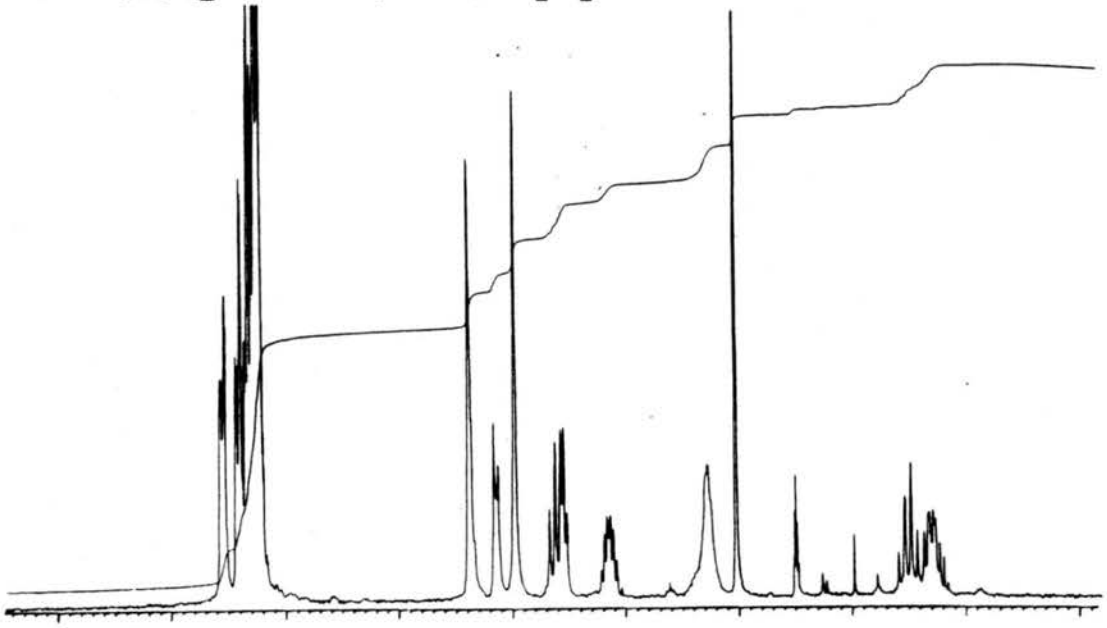
^1H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 2.4-2.7(2H, m); 3.2-3.5(2H, m); 4.29(1H, broad s); 4.54(1H, broad t, J=9Hz); 4.68(1H, broad t, J=5Hz); 4.98(2H, s); 5.10-5.13(1H, m); 5.30-5.36(2H, m); 7.15-7.65(15H, m). IR(NaCl, neat): 3500-3300, 1755, 1695, 1420 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 461.8(M^+ +1, 0.3%); 460.8(M^+, 0.1%); $[\alpha]_D^{25}$ = +9.6 (c = 1.5, CH_2Cl_2).



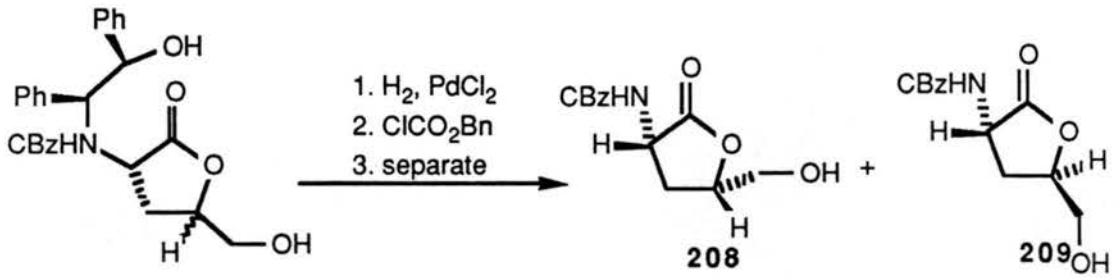
^{1}H NMR (200 MHz) of **207a** in DMSO-d_6 at 393°K.

207b

^{1}H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 1.49(1H, q, J=10.5Hz); 3.27(2H, broad s); 1.2-1.4(1H, m); 4.07-4.21(1H, m); 4.5-4.7(2H, m); 4.97(2H, s); 5.12-5.17(1H, m); 5.38(2H, m); 7.15-7.65(15H, m). IR(NaCl, neat): 3580, 3500-3300, 3050, 2950, 1760, 1695, 1450, 1415 cm^{-1}. Mass spectrum (NH_3)(CI): m/e = 461.7(M^+ +1, 0.1%); $[\alpha]_D^{25}$ = +59.9 (c = 1.4, CH_2Cl_2).



^{1}H NMR (200 MHz) of **207b** in DMSO-d_6 at 393°K.



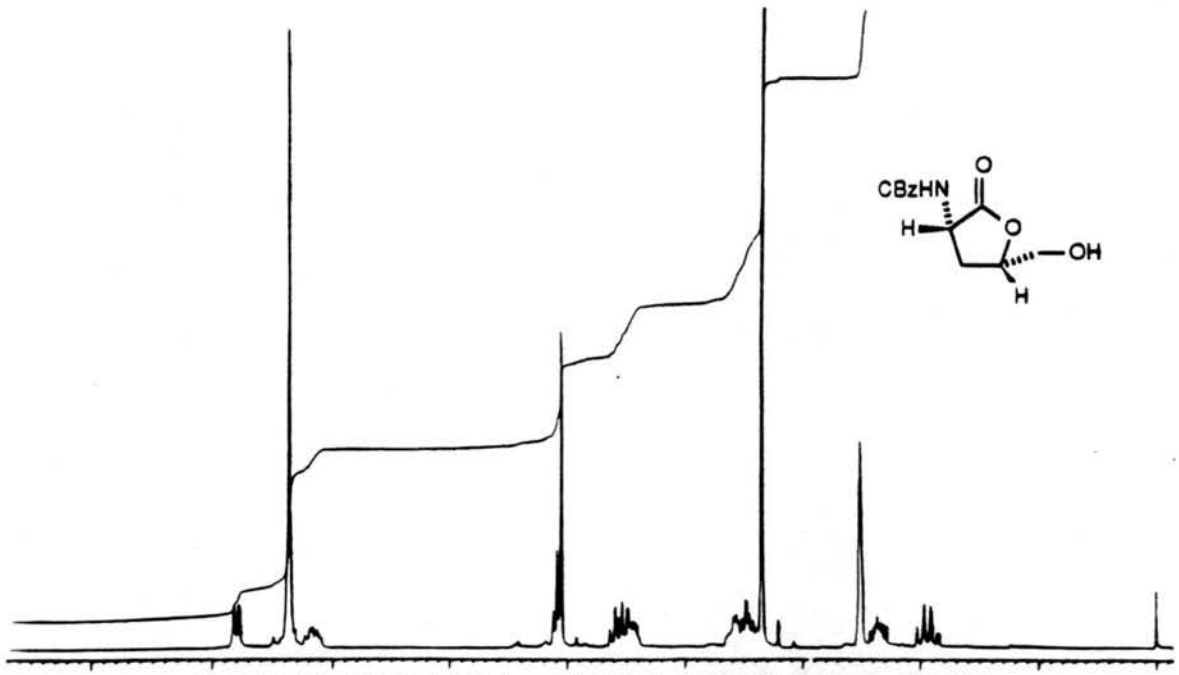
207 **208** **209**

(2S,4S)-2-[(Benzyloxycarbonyl)amino]-4-hydroxymethyl-4-hydroxybutyric acid-γ-lactone (208) and (2S,4R)-2-[(Benzyloxycarbonyl)amino]-4-hydroxymethyl-4-hydroxy-butyric acid -γ-lactone (209)

To a stirred solution of **207** (103 mg, 0.223 mmol, 1 equiv) in 1:1 THF/EtOH (4 mL) was added $PdCl_2$ (23 mg, 0.067 mmol, 0.3 equiv). The mixture was hydrogenated 48 hours at 40 psi. The mixture was then purged with nitrogen, filtered through celite, concentrated and triturated with Et_2O leaving 38 mg (130%) of an off-white solid. The crude material was dissolved in 1 mL dry DMF. To this stirred solution was added Et_3N (80 μL, 0.58 mmol, 2 equiv) followed by addition of benzyl chlorformate (52 μL, 0.348 mmol, 1.2 equiv). After 22 h the DMF was removed in vacuo and the mixture was separated by pTLC on silica gel (eluted with 3:2 EtOAc/hexanes) to afford 12.3 mg (21%) **208** and 8.8 mg (14.9%) **209**. % ee **208** ≥89% (Figure 27b).

208

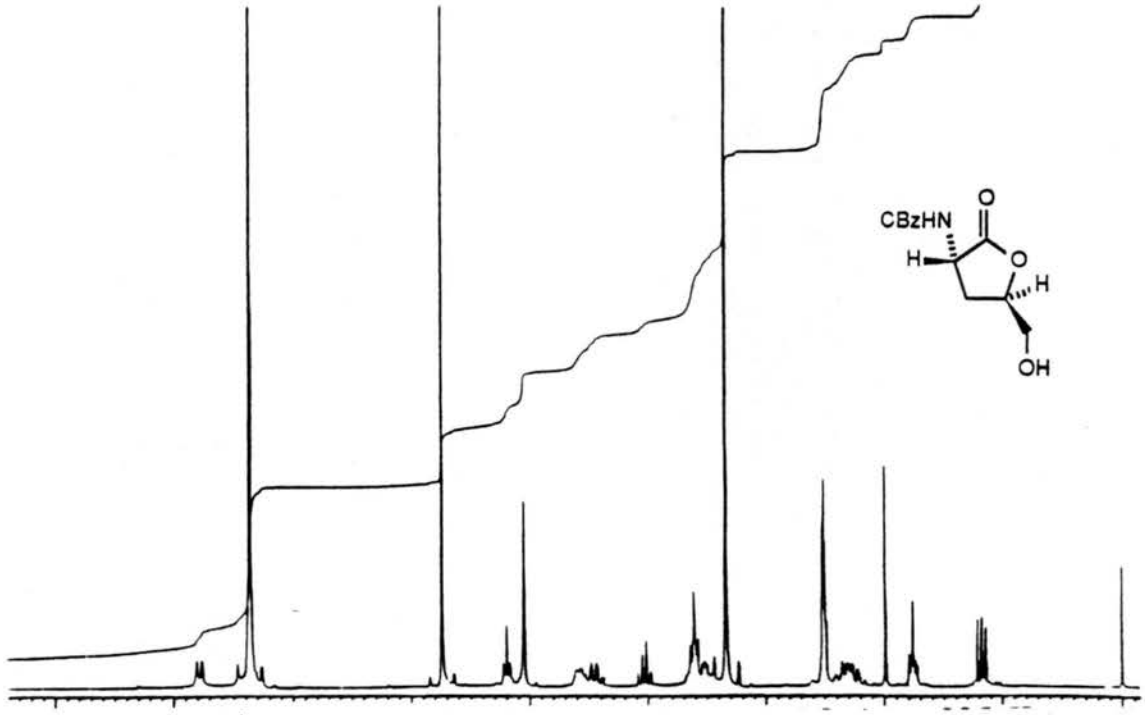
^1H NMR (200 MHz) (DMSO-d_6) δ $(CH_3)_4Si$: 4.93(1H, q, J=11.8Hz); 2.28-2.42(1H, m); 3.40-3.65(2H, m); 4.41-4.63(2H, m); 5.05-5.12(3H, m); 7.36(5H, s); 7.81(1H, d, J=8.5Hz). IR(KBr): 3370, 3280, 1780, 1690, 1530, 1520, 1450, 1370, 1320, 1280, 1255, 1180, 1050 cm^{-1}, mp 109-110° (recrystallized EtOAc/hexanes) $[\alpha]_D^{25}$ = -1.0 (c = 0.6, MeOH). (Authentic **208** isolated from PTLC: $[\alpha]_D^{25}$ = -1.0 (c = 0.6, MeOH).



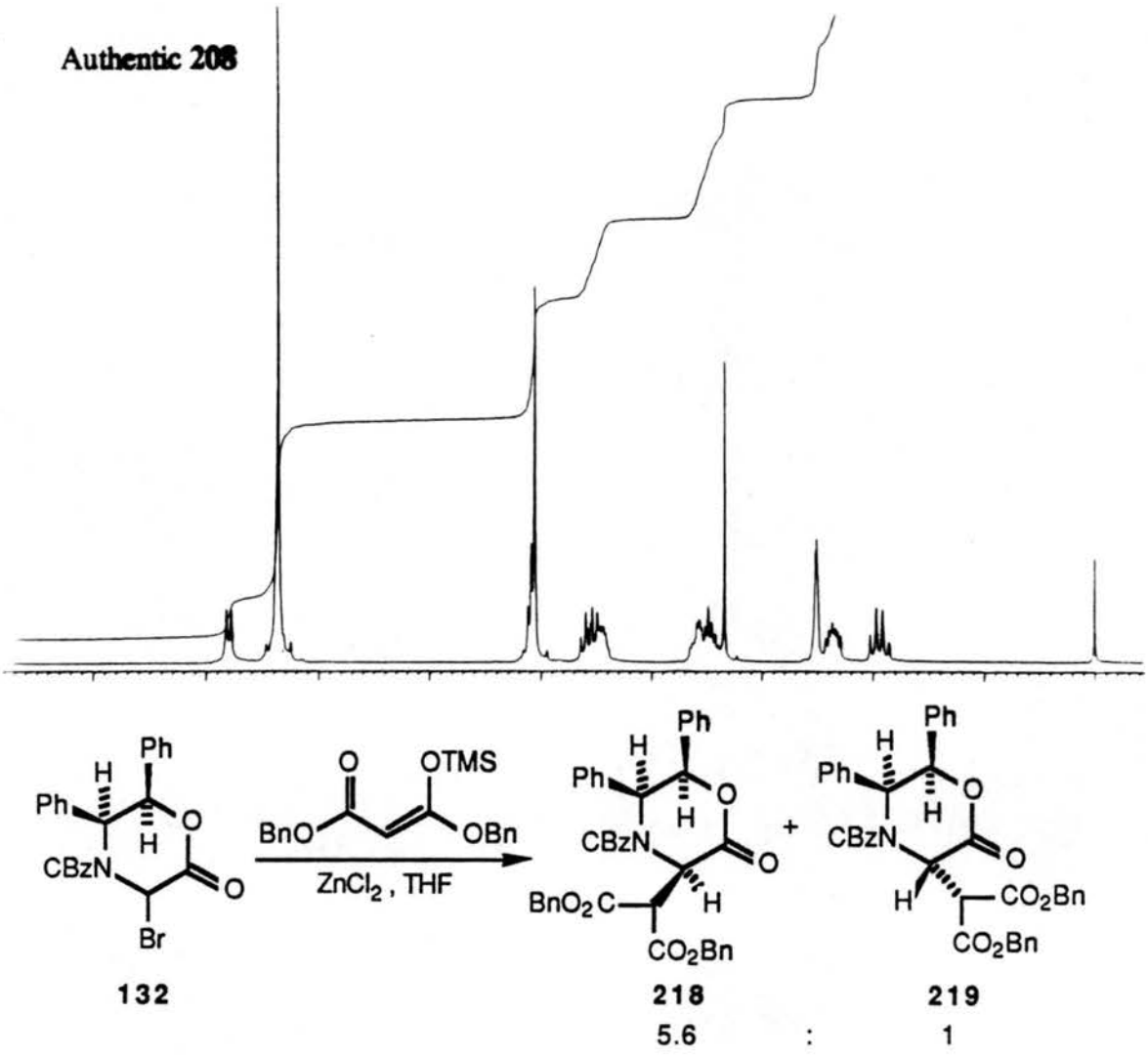
^{1}H NMR (200 MHz) of **208** in DMSO-d_6 at 295°K.

209

^{1}H NMR (200 MHz) (DMSO-d_6) δ DMSO: 2.1-2.4(2H, m); 3.42-3.64(2H, m); 4.43(1H, q, J=9.7Hz); 4.5-4.65(1H, m); 5.03(2H, s); 5.19(1H, t, J=5.3Hz); 7.35(5H, s); 7.78(1H, d, J=8.5Hz), mp 124° (recrystallized EtOAc/hexanes) $[\alpha]_D^{25}$ = -75.0 (c = -0.2, MeOH).



^{1}H NMR (200 MHz) of **209** in DMSO-d_6 at 295°K.



132 **218** : **219**

5.6 : 1

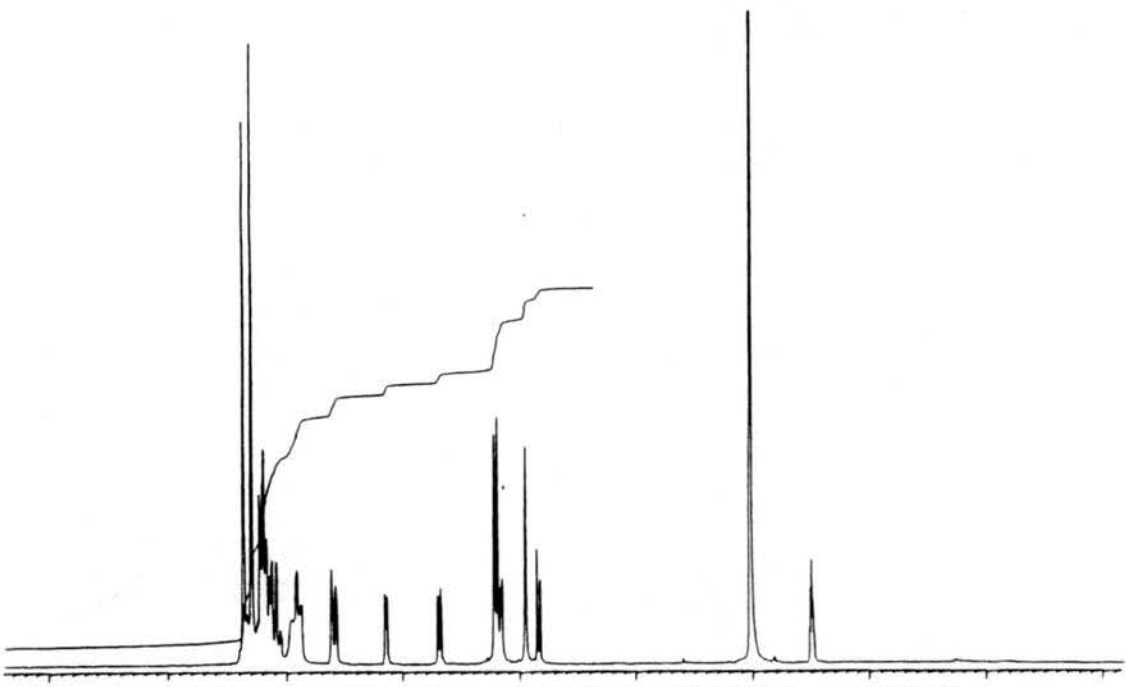
(3R,5S,6R)-4-Benzyloxycarbonyl-3-(dibenzylmalonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (218) and (3S,5S,6R) (3S,5S,6)-4-Benzyloxycarbonyl-3-(dibenzyl-malonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (219)

To a stirred solution of dibenzylmalonate[78] (410 μL, 1.85 mmol, 2.8 equiv) in dry THF (6 mL) at 0°C was added NaH (88 mg, 1.85 mmol, 2.8 equiv, 50% dispersion in oil). After 25 min trimethylchlorosilane (245 μL, 1.94 mmol, 3 equiv) was added to the enolate. The mixture was stirred at 0°C for 20 min, at room temperature for 25 min, and then added to a solution of **133** (300 mg, 0.65 mmol, 1 equiv) in dry THF (8 mL) via syringe. To the light yellow solution was added $ZnCl_2$ (400 μL, 0.77 mmol, 1.2 equiv,

1.95M in THF) turning the mixture orange. After 4 h the reaction mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, passed through a plug of silica gel, concentrated and separated by HPLC on Whatman portisil 10 silica column (50 cm) (eluted with 1:5 EtOAc/hexanes at 5 ml/min) affording 36.5 mg (8%) **218** and 207 mg (46%) **219**.

219 (solid)

^{1}H NMR (200 MHz) (DMSO=-d_6)(393°K) δ DMSO: 4.83(1H, d, J=5.0Hz); 4.95(2H, s); 5.16(1H, d, J=3Hz); 5.19(2H, s); 5.22(2H, s); 5.68(1H, d, J=5Hz); 6.14(1H, d, J=3Hz); 6.57(1H, s); 6.61(1H, s); 6.8-6.9(4H, m); 7.1-7.4(19H, m). IR(KBr): 3060, 3030, 2940, 1750, 1735, 1700, 1495, 1450, 1390, 1345, 1315, 1275, 1215, 1175, 1140, 1105 cm^{-1}. Mass spectrum (NH_3)(CI): 687.9M$^+$ +18, 0.7%); 670.3(M$^+$, 1.4%); 579.0(M$^+$ +91, 1.1%), mp 168.3-168.9 (recrystallized EtOAc/hexanes), $[\alpha]_D^{25}$ = +23.8 (c = 1.14, CH_2Cl_2).

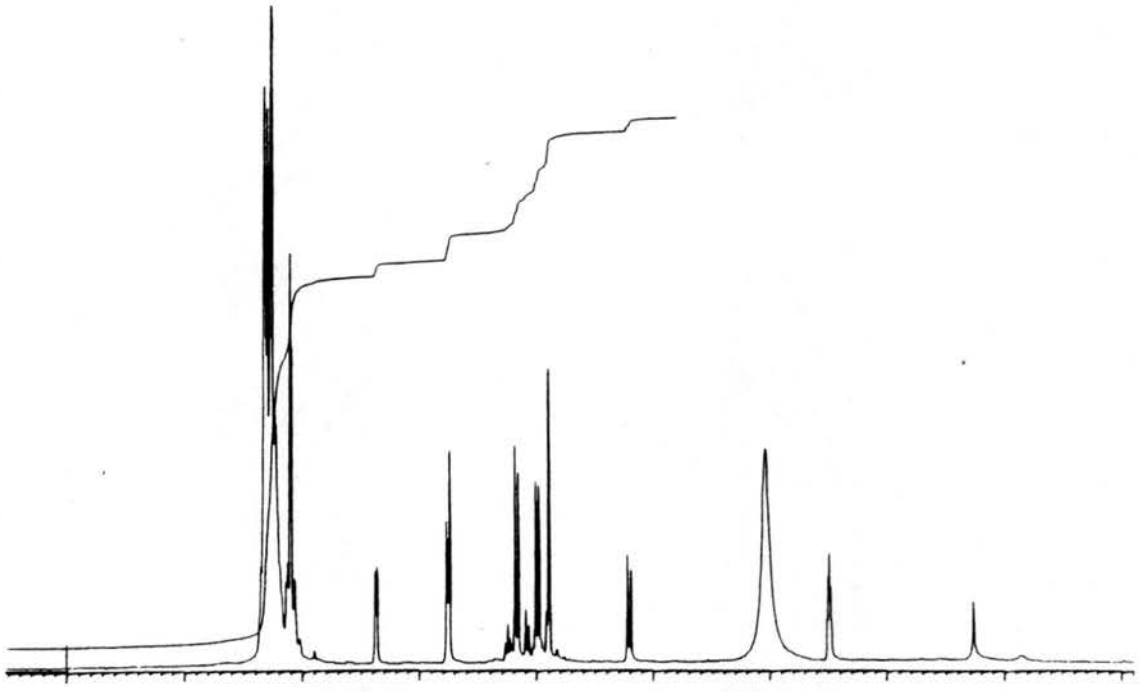


^{1}H NMR (200 MHz) of **219** in DMSO-d_6 at 393°K.

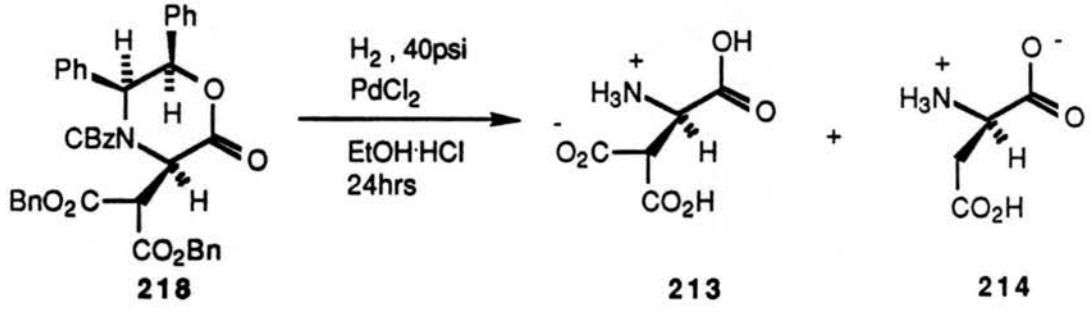
218 (oil)

^{1}H NMR (200 MHz) (DMSO-d_6) (393°K) δ DMSO: 4.19(1H, d, J=5.5Hz); 4.89(2H, s); 4.98(2H, ABq, J=12.7Hz); 5.17(2H, ABq, J=12.5Hz); 5.74(1H, d,

J=3.2Hz); 5.75(1H, d, J=5.5Hz); 6.37(1H, d, J=3.2Hz); 7.0-7.4(25H, m). IR(NaCl, neat): 3050, 2980, 1740, 1700, 1495, 1445, 1415, 1395, 1205, 1140 cm^{-1}. Analysis calculated for $C_{41}H_{35}NO_8$: C, 73.53; H, 5.27; N, 2.09. Found: C, 73.43; H, 5.40; N, 2.16. $[\alpha]_D^{25} = +60.6$ (c = 1.51, CH_2Cl_2).



^1H NMR (200 MHz) of **218** in DMSO-d_6 at 393°K.



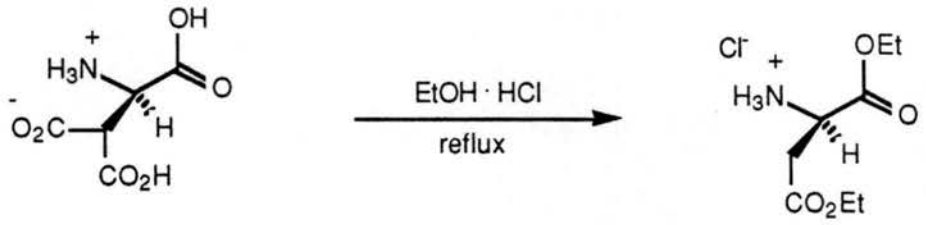
218 **213** **214**

(R)-β-Carboxyaspartic Acid (213)

To a solution of **218** (77.6 mg, 0.12 mmol, 1 equiv) in THF (1.5 mL) and EtOH·HCl (1.5 mL, ~0.03N) was added $PdCl_2$ (11.8 mg, 0.03 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 27 h, purged with N_2, filtered through celite to

white solid. Dissolved crude mixture in 4 mL water (HPLC grade) and stirred with ion exchange resin (600 mg wet weight, Dowex 50W-X8 H^+ form washed with 1N NaOH, H_2O, 10% H_2SO_4, H_2O until pH ~6, THF, then H_2O) for 15 min. The filtered mixture was passed through C18 cartridge (Millipore C18 SEPPAK wet first with CH_3CN then with water) and concentrated <u>in vacuo</u> yielding 8 mg white solid.

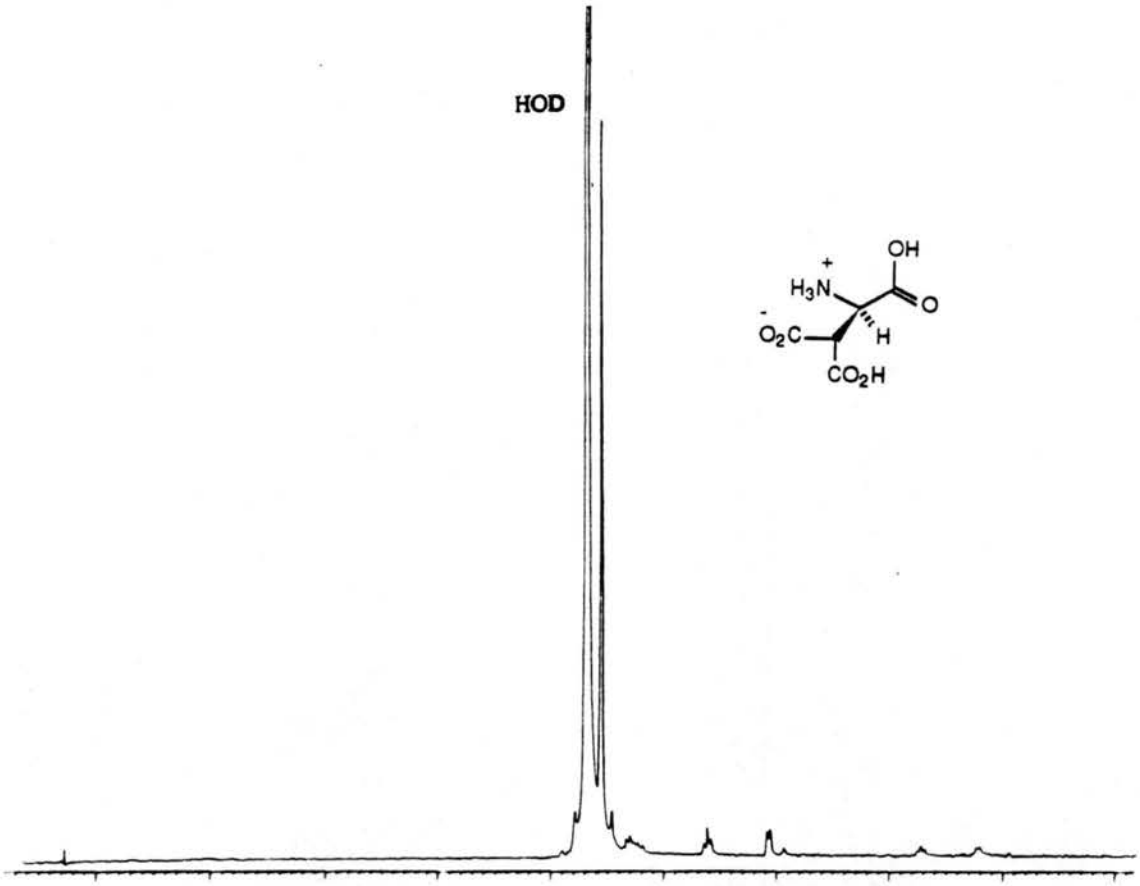
$[\alpha]_D^{25}$ = -13.2 (c = 0.8, H_2O); $[\alpha]_D^{25}$ = -13.1 (c = 0.8, D_2O).



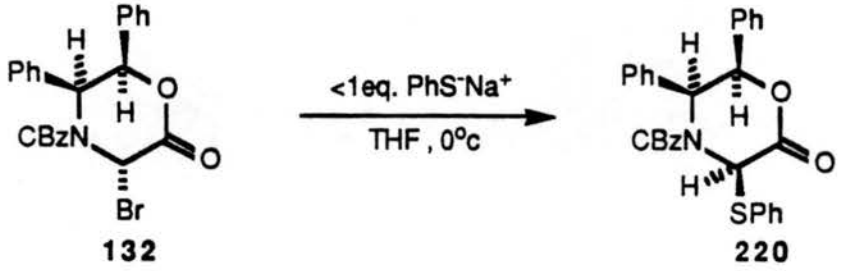
213 **139**

(R)-Diethylaspartate (139)

EtOH·HCl (2.5 mL, 1N) was added to **213** (8 mg, 0.35 mmol) and the mixture was heated and maintained at reflux for 3 h. The mixture was cooled, concentrated and diluted with $CHCl_3$ and concentrated 2x to remove excess HCl, leaving approximately 8 mg white solid, % ee ≥98 (Figure 28a).



^{1}H NMR (200 MHz) of **213** in D_2O at 295°K.



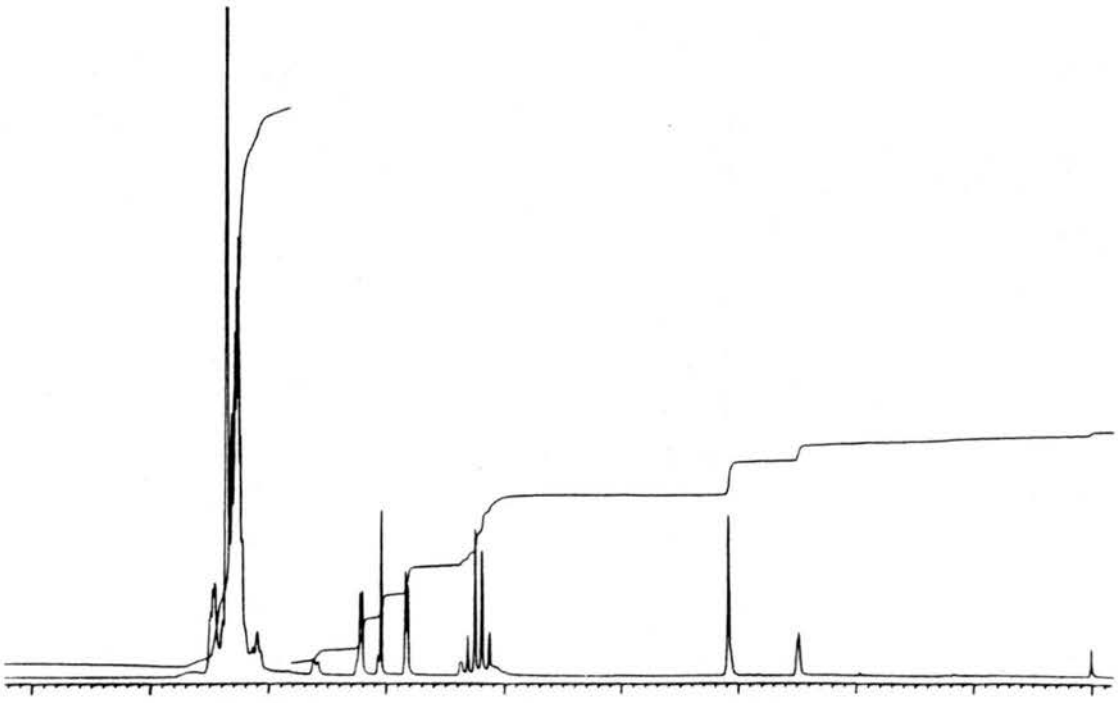
132 **220**

(3R,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(phenylthio)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (220)

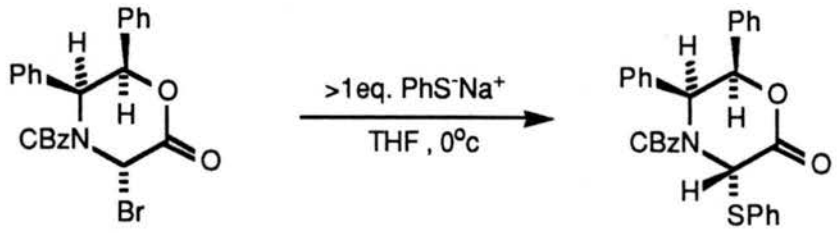
To a stirred solution of thiophenol (17 μL, 0.16 mmol, 0.5 equiv) in THF (1 mL) at 0°C was added NaH (8 mg, 0.16 mmol, 0.5 mg). After 10 min the resultant suspension was added to a solution of **133a** (150 mg, 0.32 mmol, 1 equiv) in THF (3 ml) at 0°C via syringe. After 2 min the mixture was quenched, diluted with water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium

sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford 62.8 mg (79% based on thiophenol) **220** as a yellowish solid.

^{1}H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 5.20(2H, ABq, J=12.4Hz); 5.81(1H, d, J=3.6Hz); 6.03(1H, s); 6.19(1H, d, J=3.6Hz); 7.0-7.5(20H, m). IR(KBr): 1760, 1695, 1405, 1300, 1275, 1225 cm^{-1}. Mass spectrum (NH_3)(CI): 512.6(M^+ +18, 4.5%); 495.7(M^+ +1, 0.6%); 494.8(M^+, 0.2%), mp 158-160°c (recrystallized EtOAc/hexanes), $[\alpha]_D^{25}$ = +93.6 (c = 1.04, CH_2Cl_2).



^{1}H NMR (200 MHz) of **220** in DMSO-d_6 at 393°K.

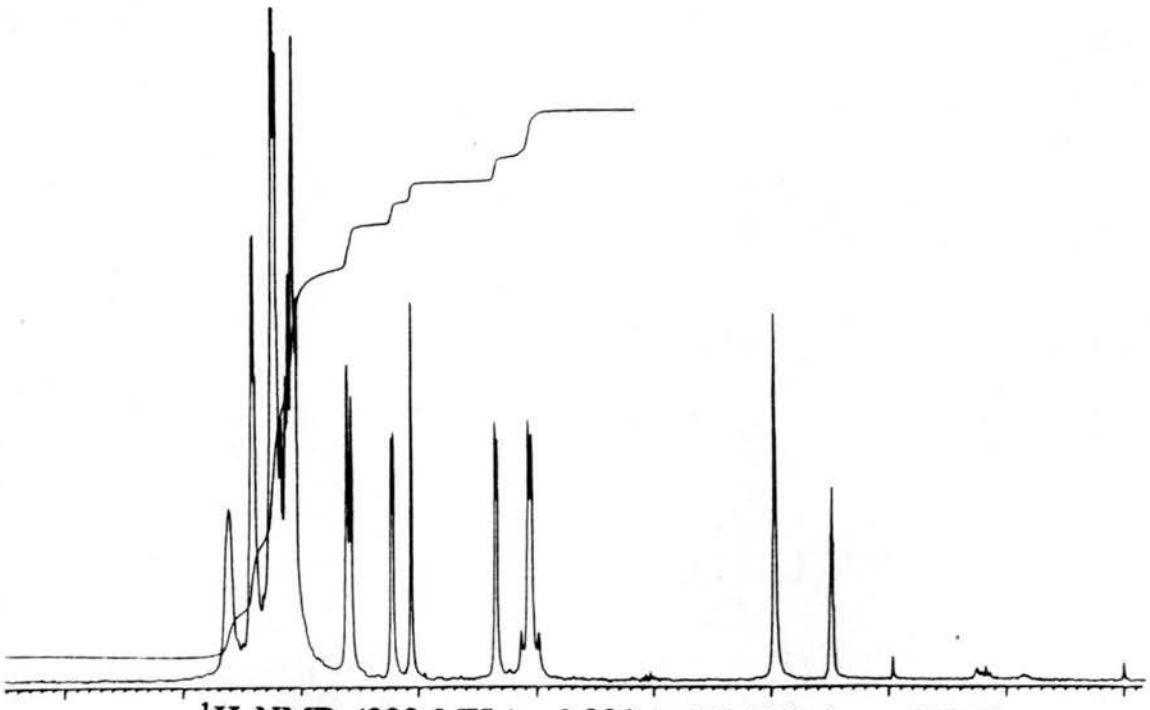


132 **221**

(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(phenylthio)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (221)

To a stirred suspension of NaH (37 mg, 0.78 mmol, 1.2 equiv, 50% dispersion in oil) in THF (3 mL) at 0°C was added the thiophenol (80 μL, 0.71 mmol, 1.1 equiv) via syringe. After 5 min the resultant white suspension of sodium thiophenolate was added to a solution of **133a** (301 mg, 0.65 mmol, 1 equiv) in THF (4 mL) at 0°C via syringe. The mixture immediately turned orange and a precipitate formed. After 1 h the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford, after recrystallization (EtOAc/hexanes), 146 mg (45%) **221** as a white solid.

^{1}H NMR (200 MHz)(DMSO-d_6)(393°K) δ DMSO: 5.06(2H, ABq, J=12.5Hz); 5.54(1H, d, J=3Hz); 6.06(1H, s); 6.22(1H, d, J=3Hz); 6.58(1H, s); 6.61(1H, s); 7.0-7.8(18H, m). IR(KBr): 1745, 1710, 1385, 1340, 1290, 1265, 1245, 1045 cm^{-1}. Mass spectrum (NH_3)(CI): 512.1(M^+ +17, 0.1%), mp 171-172°C (recrystallized EtOAc/hexanes), $[\alpha]_D^{25}$ = +13.0 (c = 1.42, CH_2Cl_2).



^{1}H NMR (200 MHz) of **221** in DMSO-d_6 at 393°K.

Determination of Optical Purity, General Procedure

The amino acid (~10 mg) was refluxed in EtOH·HCl (2 mL, 1N) then cooled and concentrated. The residue was treated with (+)- or (-)-α-methoxy-α-trifluoromethyl phenylacetyl chloride (2 equiv) in 1:1 CCl_4/pyridine (400 μL). After 8 h the mixture was diluted with Et_2O and washed successively with 1N HCl, saturated $NaHSO_4$, and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated and analyzed by ^{1}H and ^{19}F NMR.

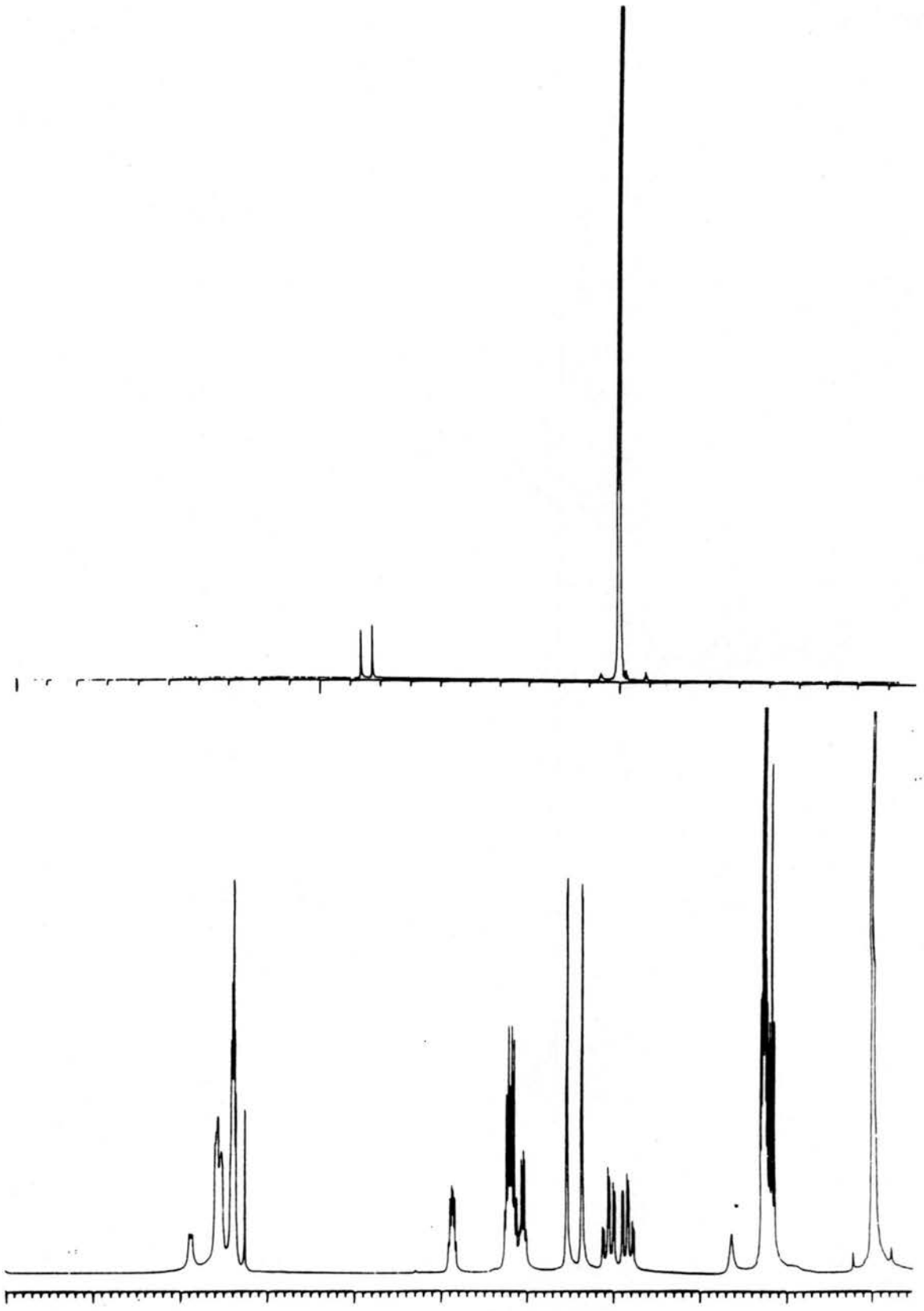


Figure 19a Racemic MPTA Diethylaspartate **139** ^{19}F and ^{1}H NMR

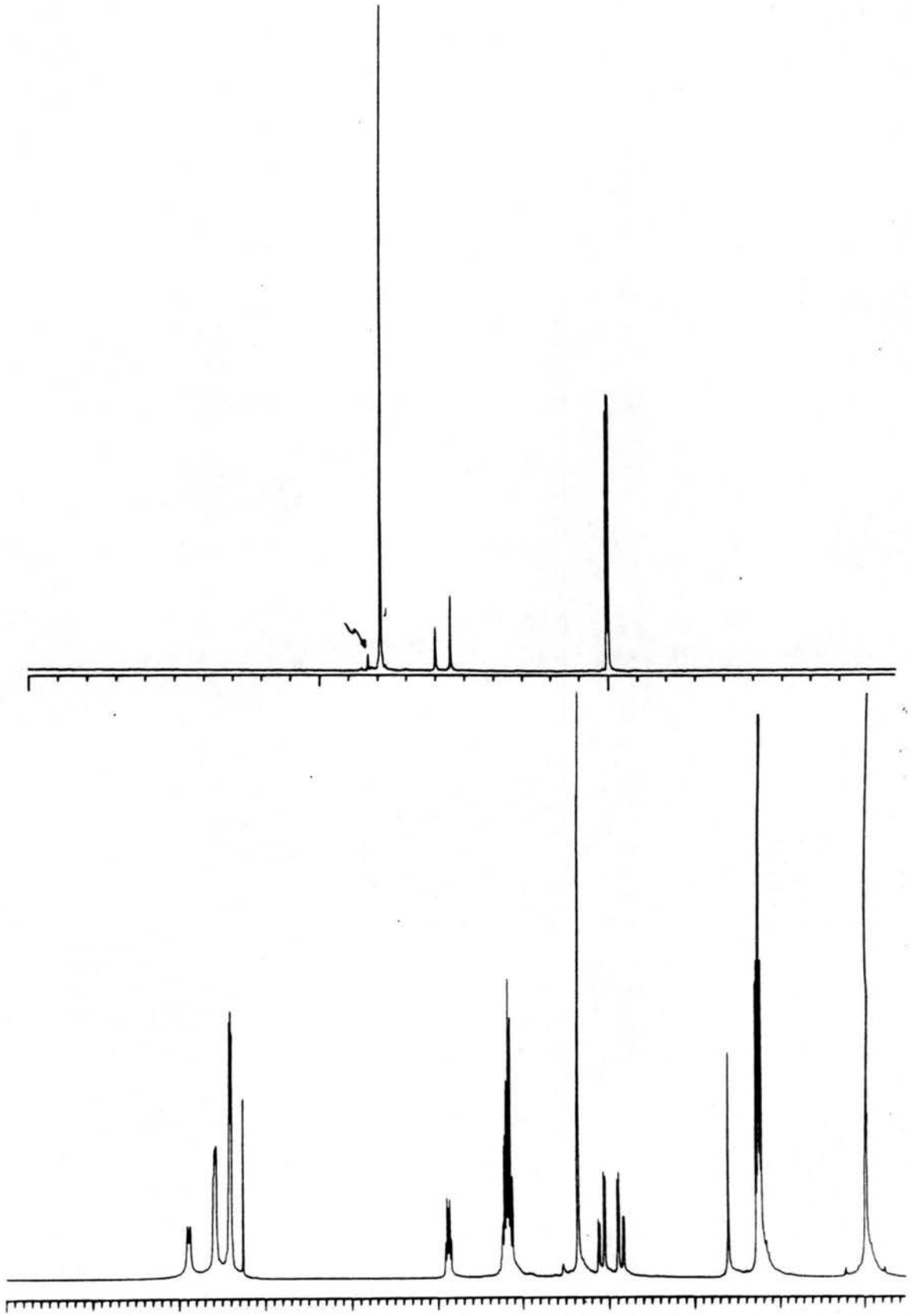


Figure 19b (-)-MPTA (Synthetic) Diethylaspartate 139 ^{19}F and ^{1}H NMR

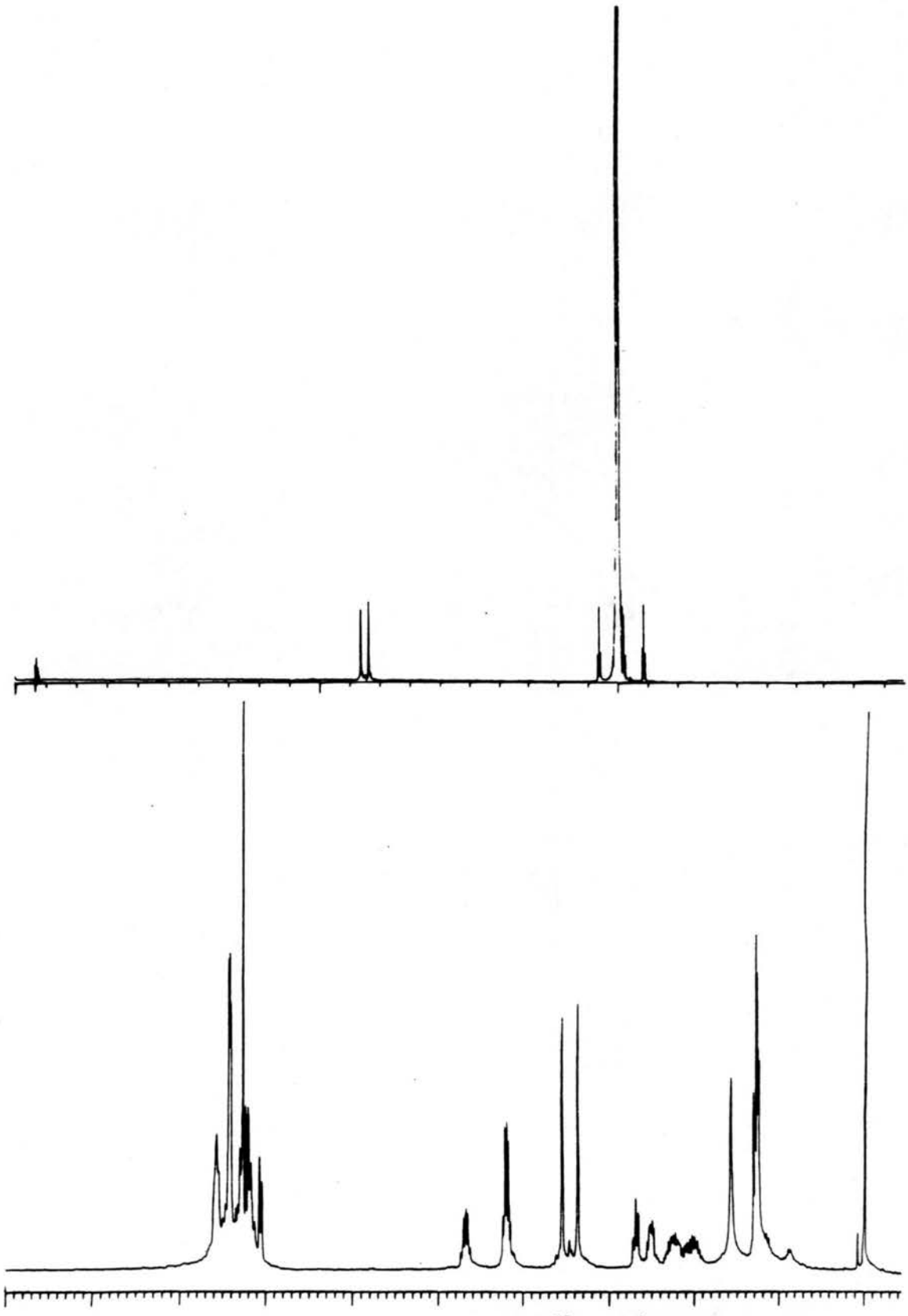


Figure 20a Racemic MPTA Homophenylalanine **142** ^{19}F and ^{1}H NMR

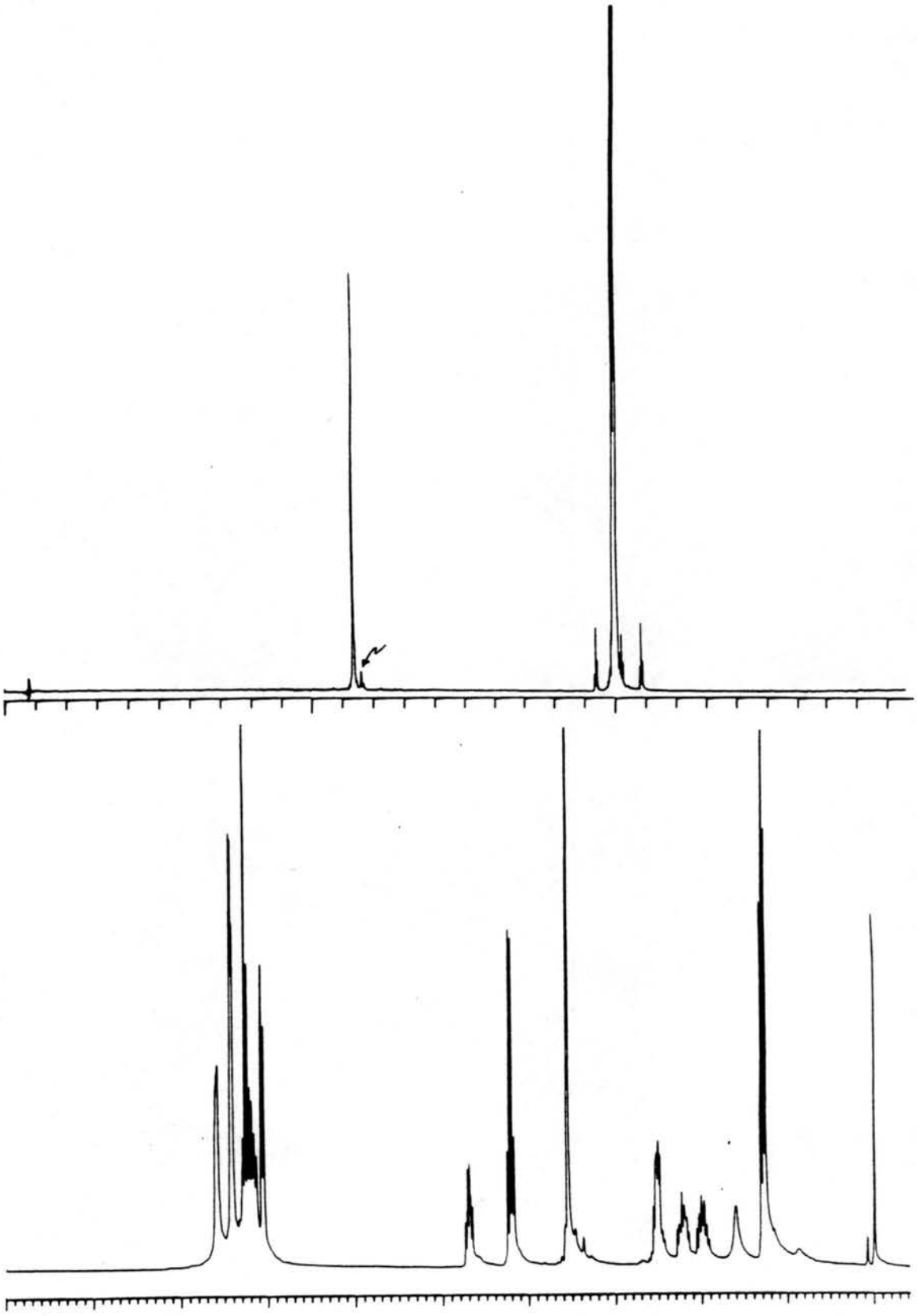


Figure 20b (-)-MPTA (Synthetic) Homophenylalanine **142** $^{19}\bar{F}$ and ^{1}H NMR

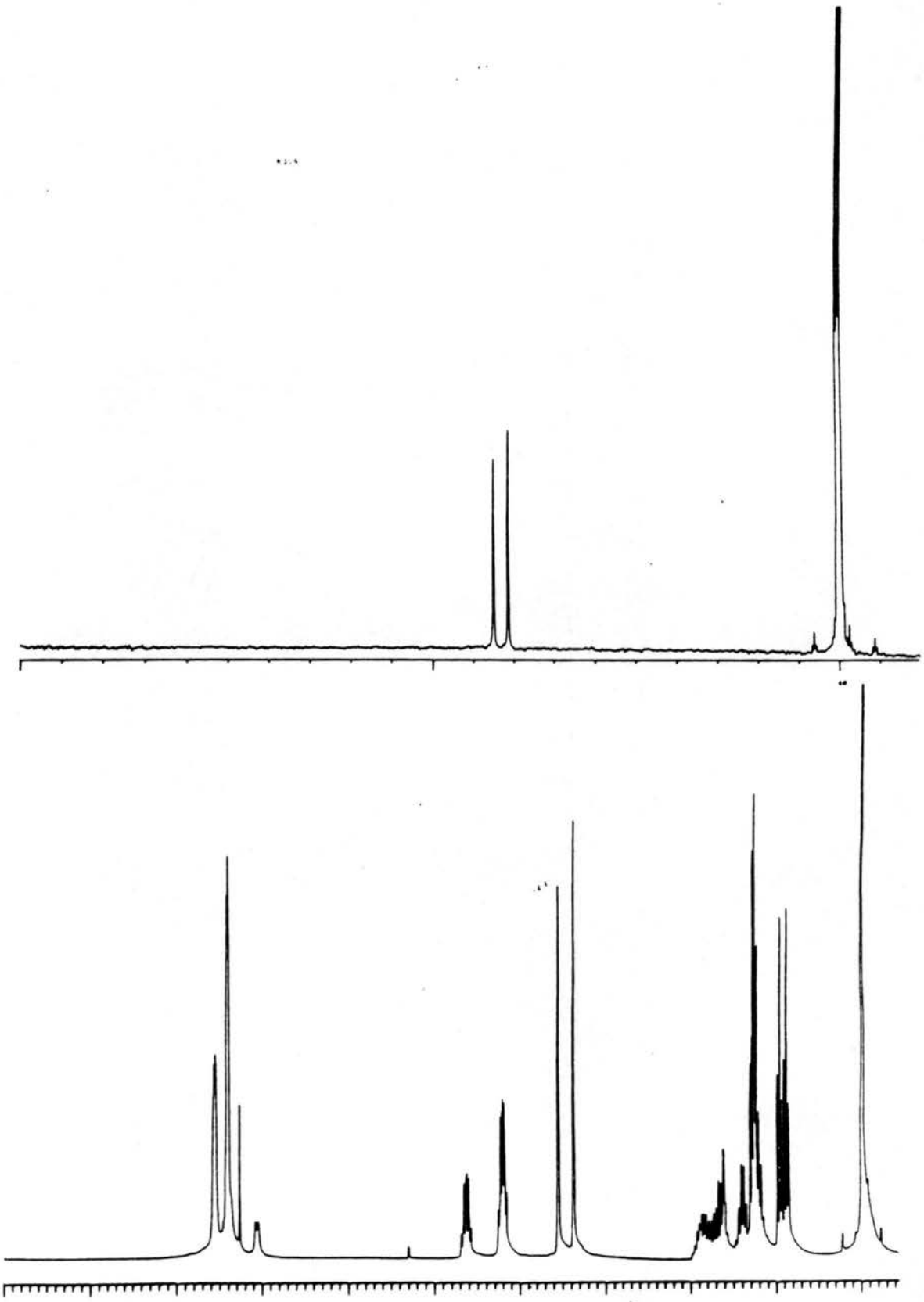


Figure 21a Racemic MPTA Norvaline 144 ^{19}F and ^{1}H NMR

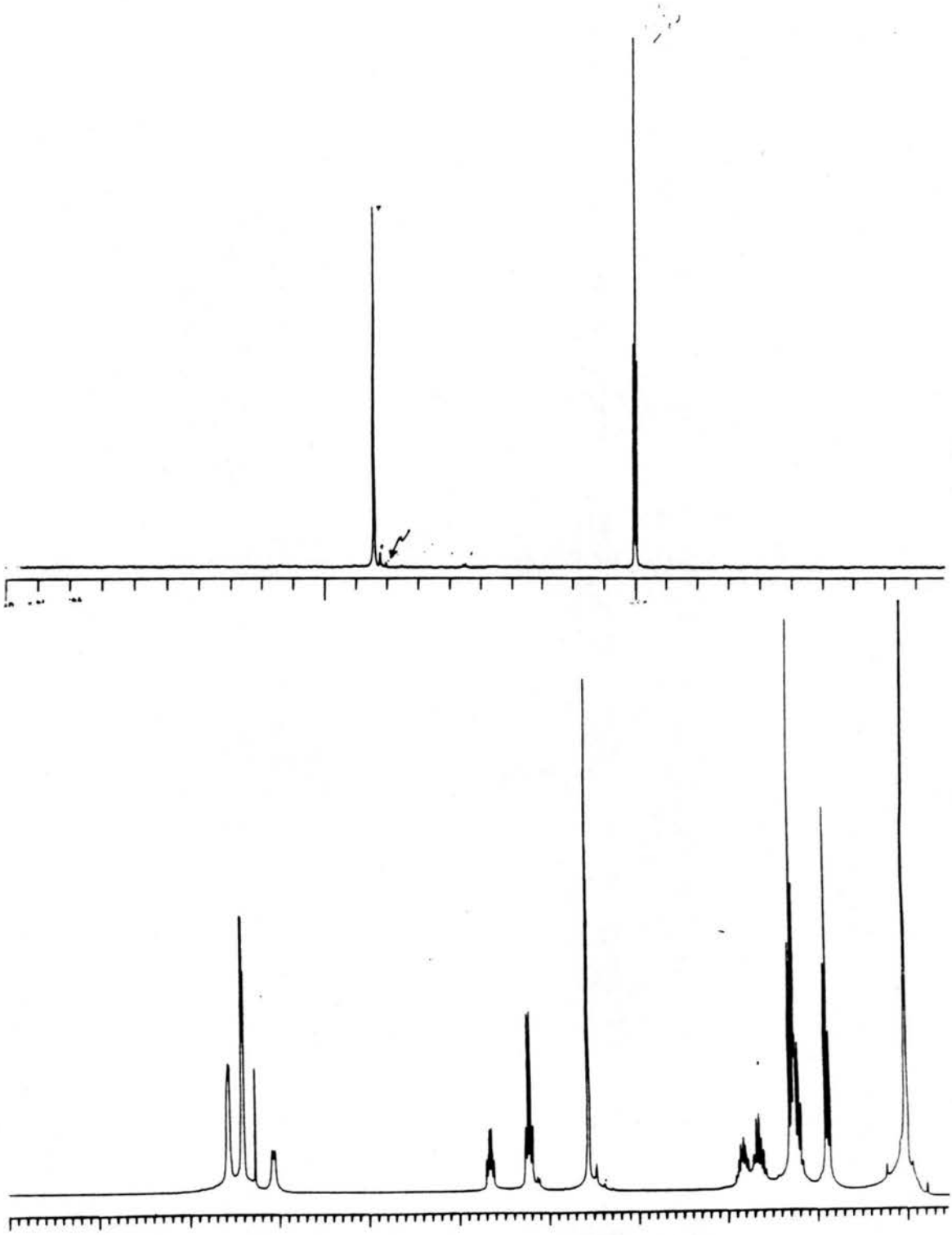


Figure 21b (-)-MPTA (Synthetic) Norvaline 142 ^{19}F and ^{1}H NMR

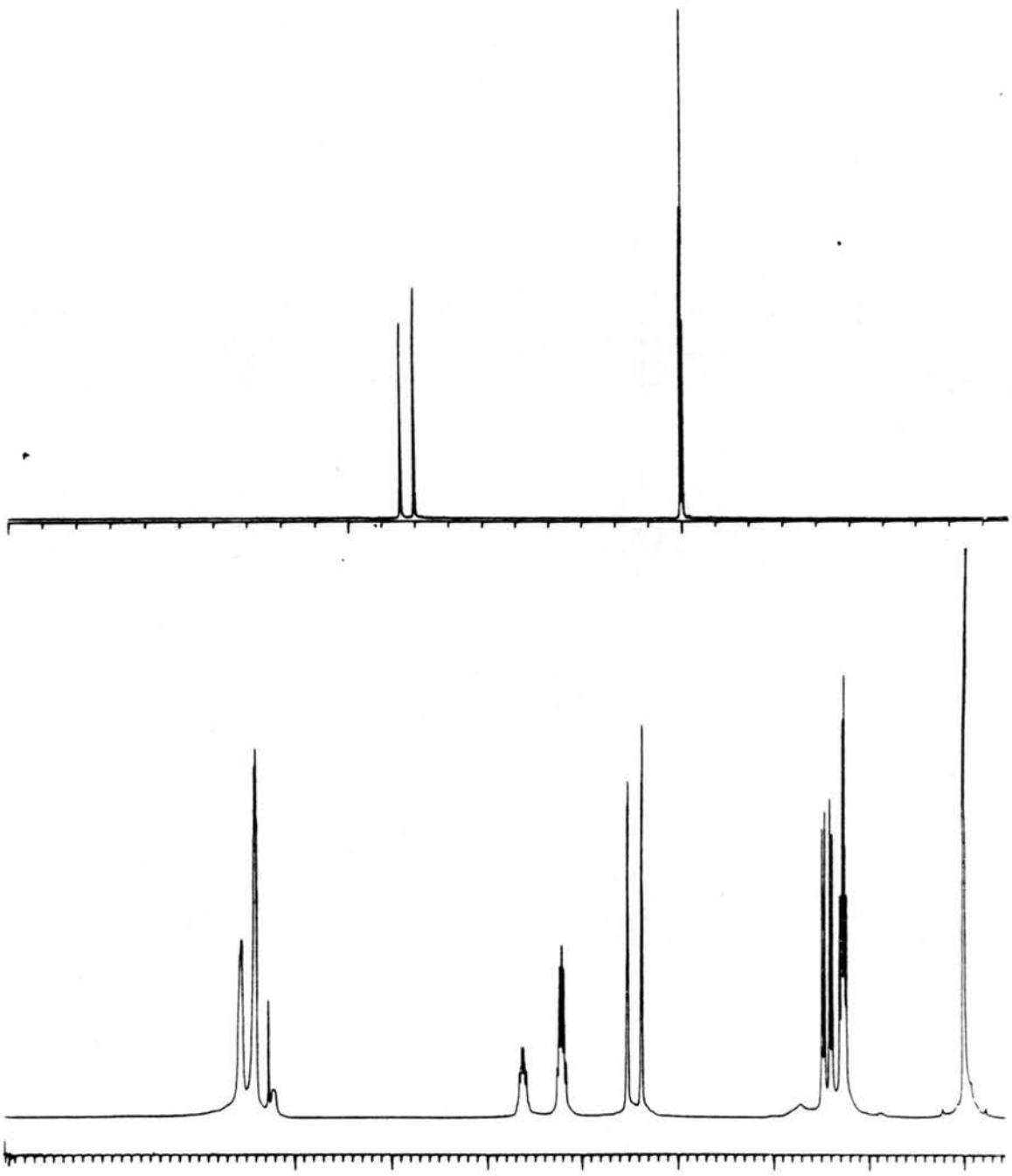


Figure 22a Racemic MPTA Alanine 147 ^{19}F and ^{1}H NMR

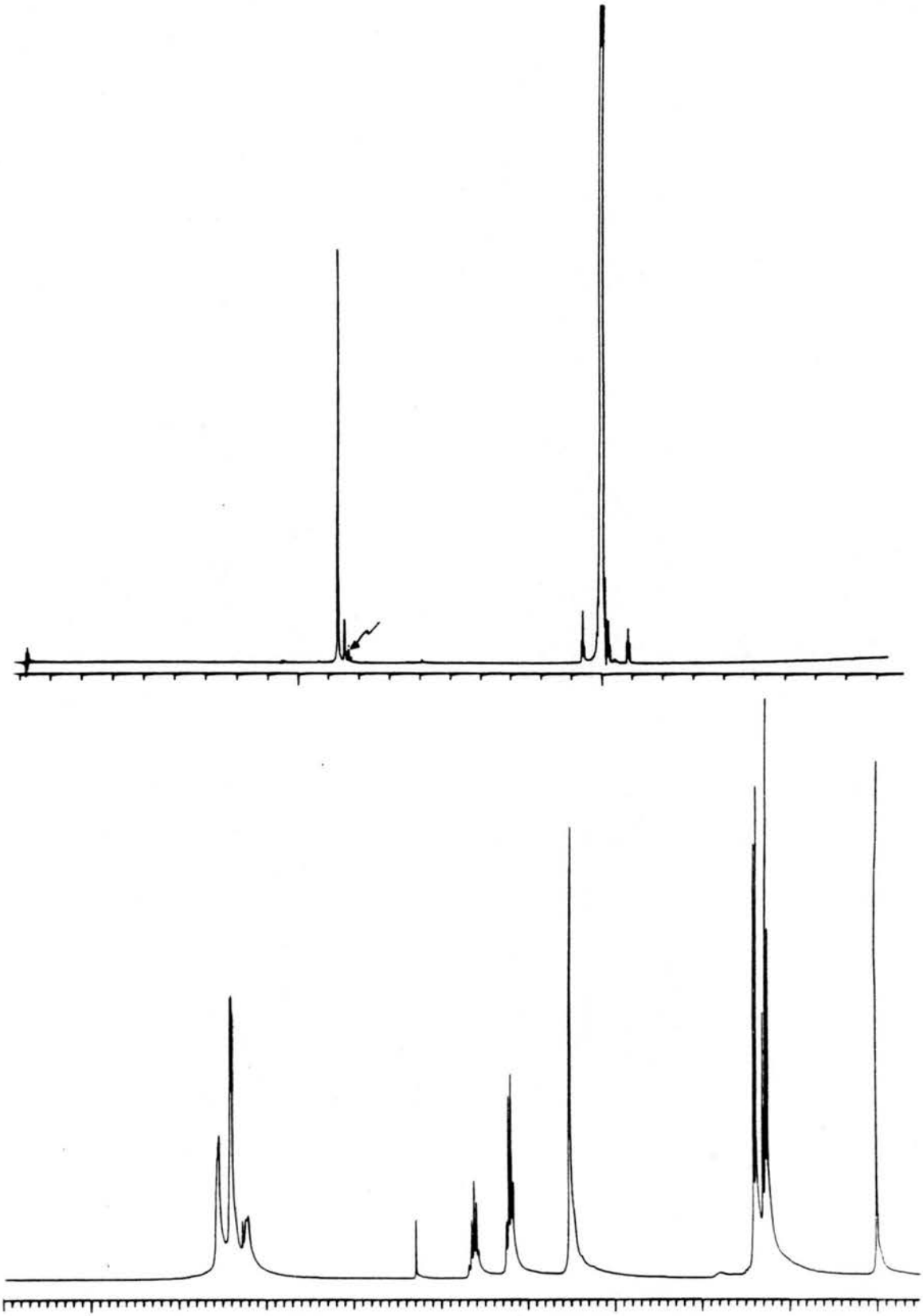


Figure 22b (-)-MPTA (Synthetic) Alanine 147 ^{19}F and ^{1}H NMR

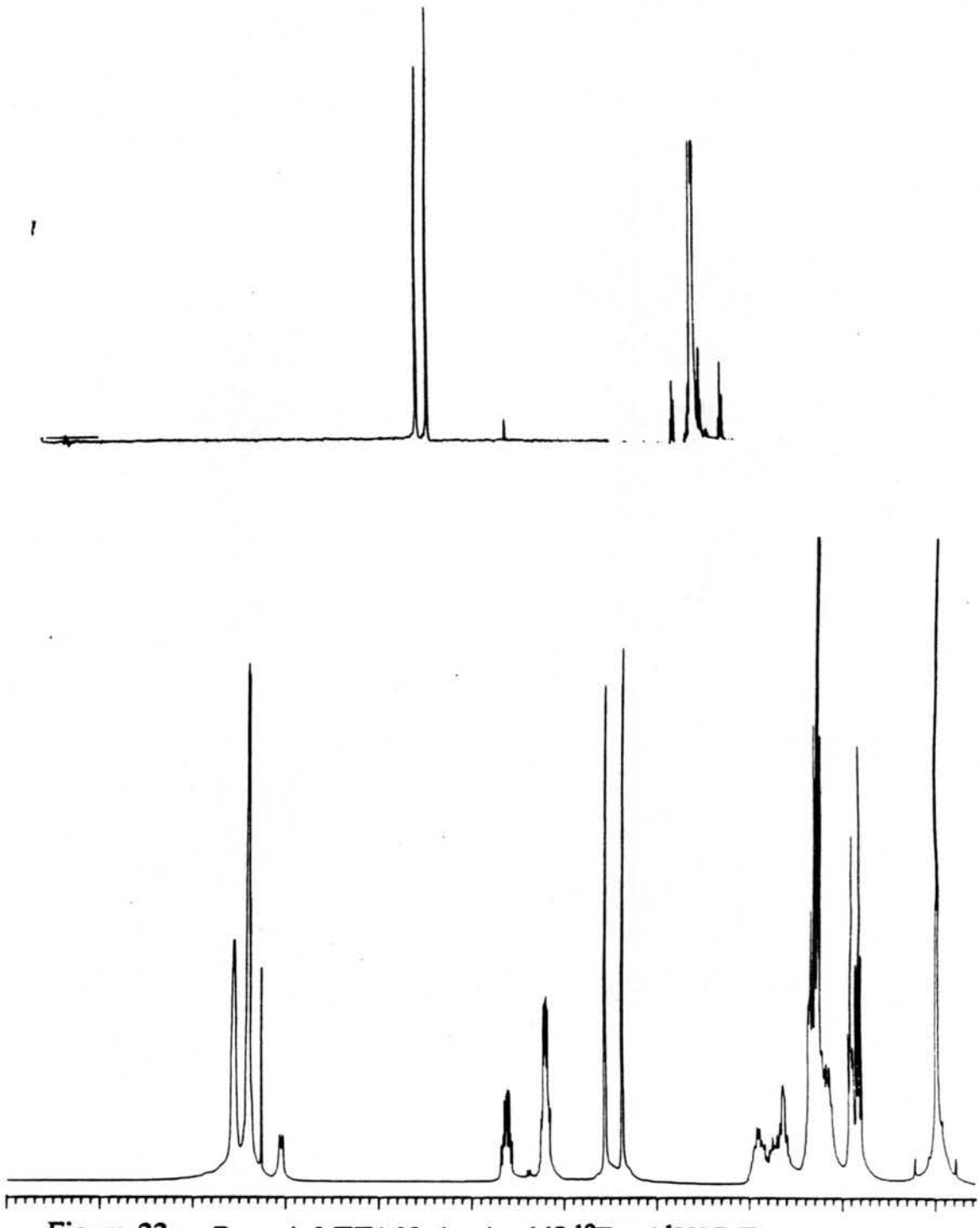


Figure 23a Racemic MPTA Norleucine **148** ^{19}F and ^{1}H NMR

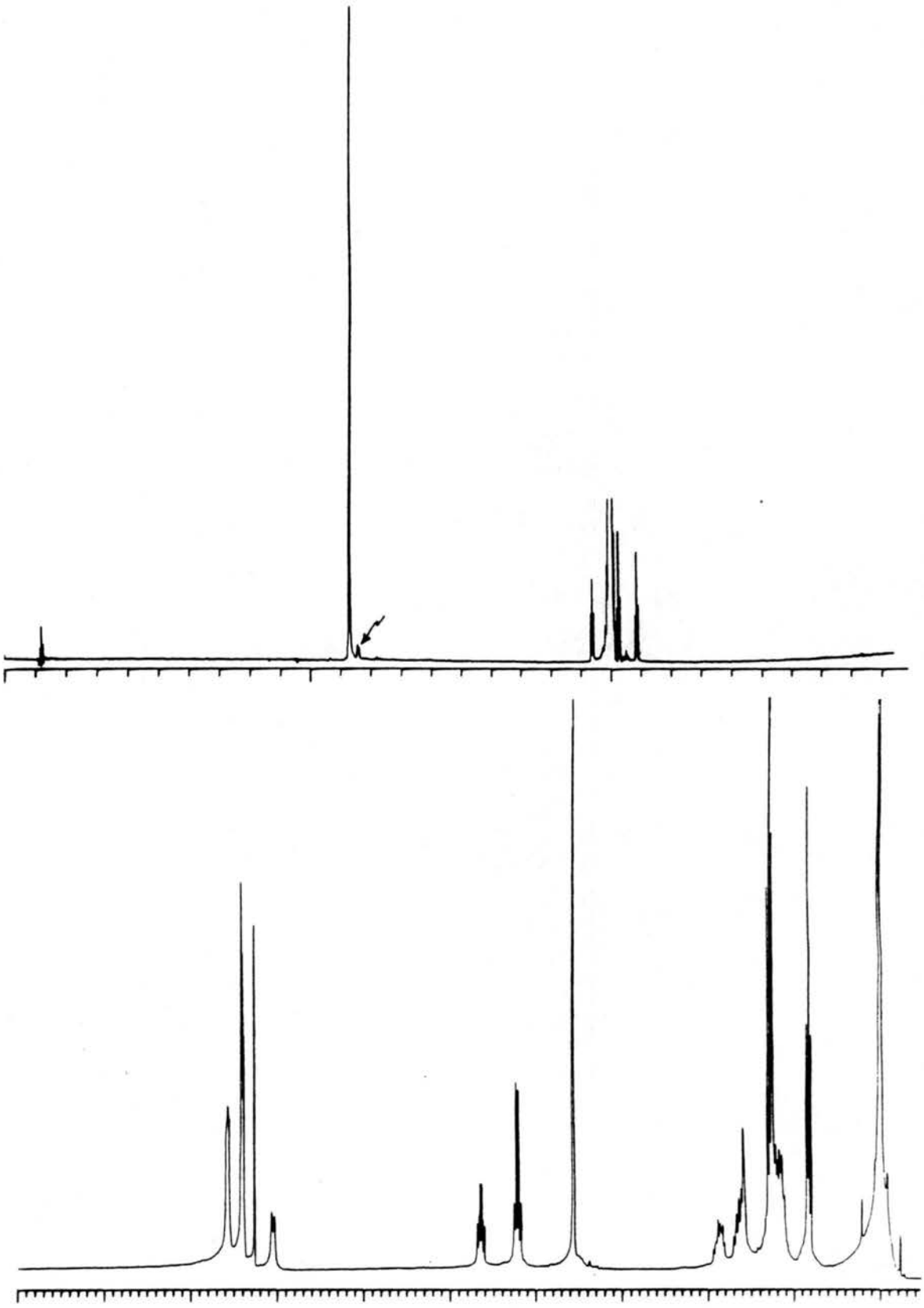


Figure 23b (-)-MPTA (Synthetic) Norleucine **148** ^{19}F and ^{1}H NMR

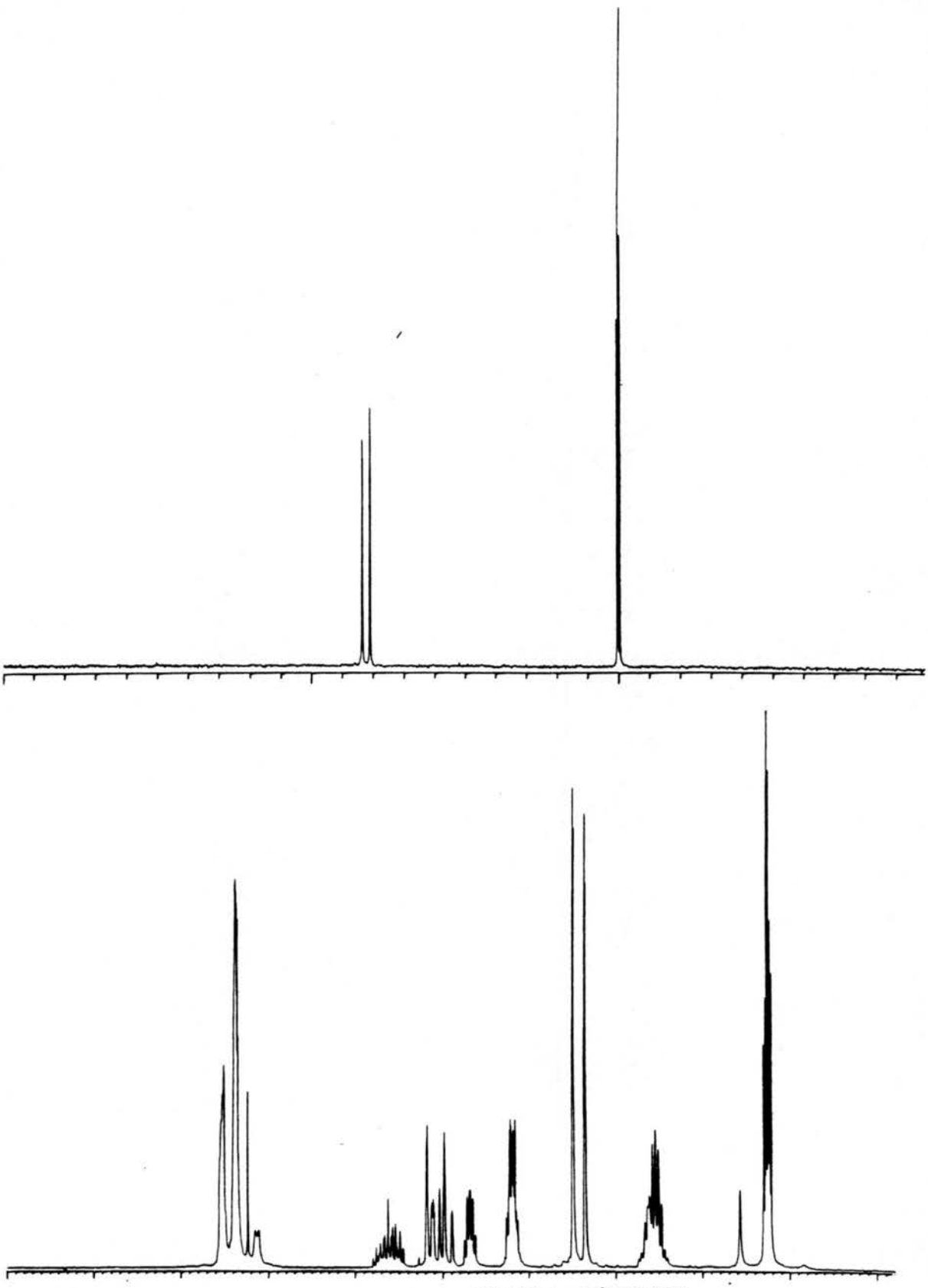


Figure 24a Racemic MPTA Allylglycine **157** ^{19}F and ^{1}H NMR

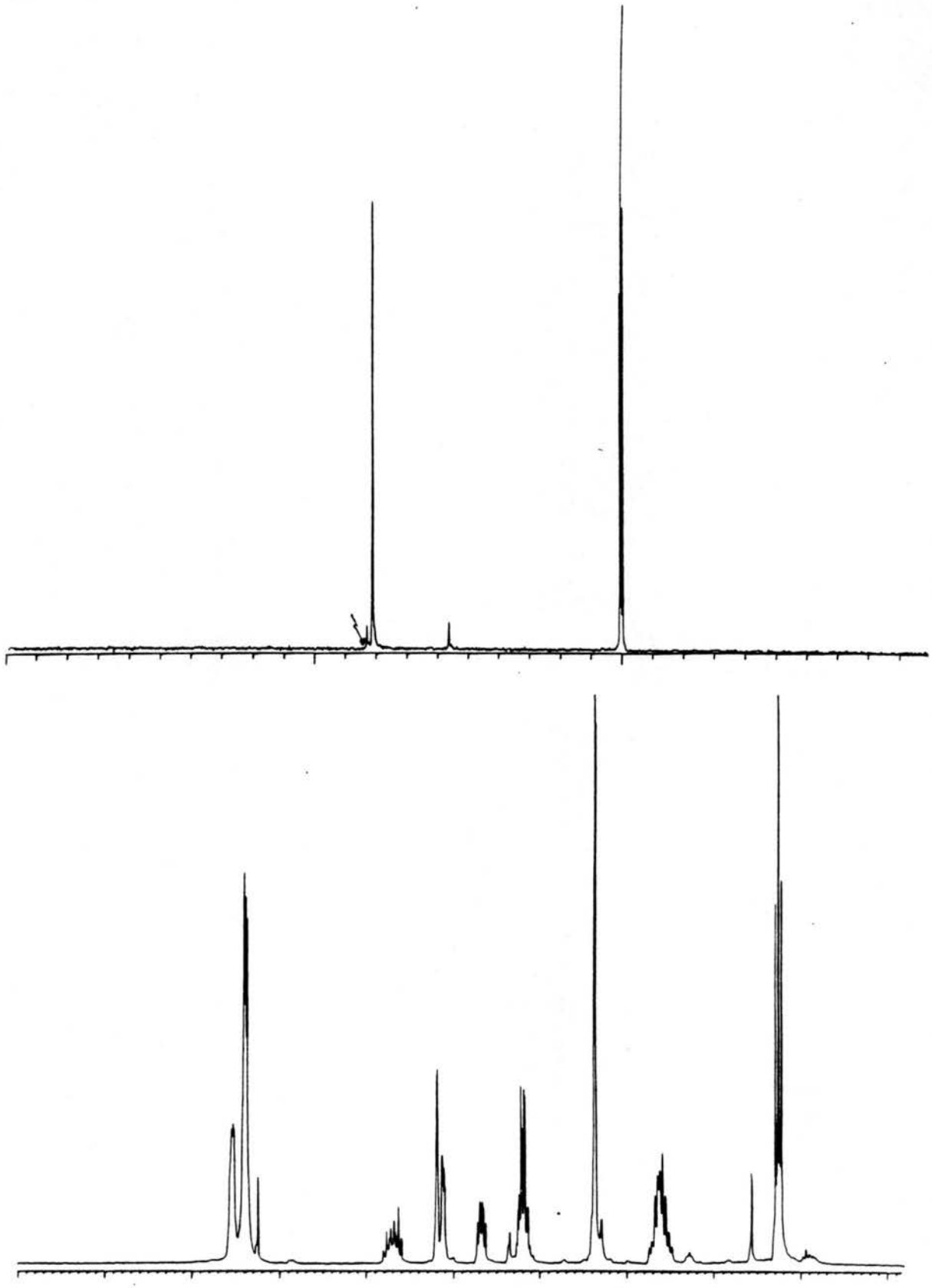


Figure 24b (+)-MPTA (Synthetic) Allylglycine **157** ^{19}F and ^{1}H NMR

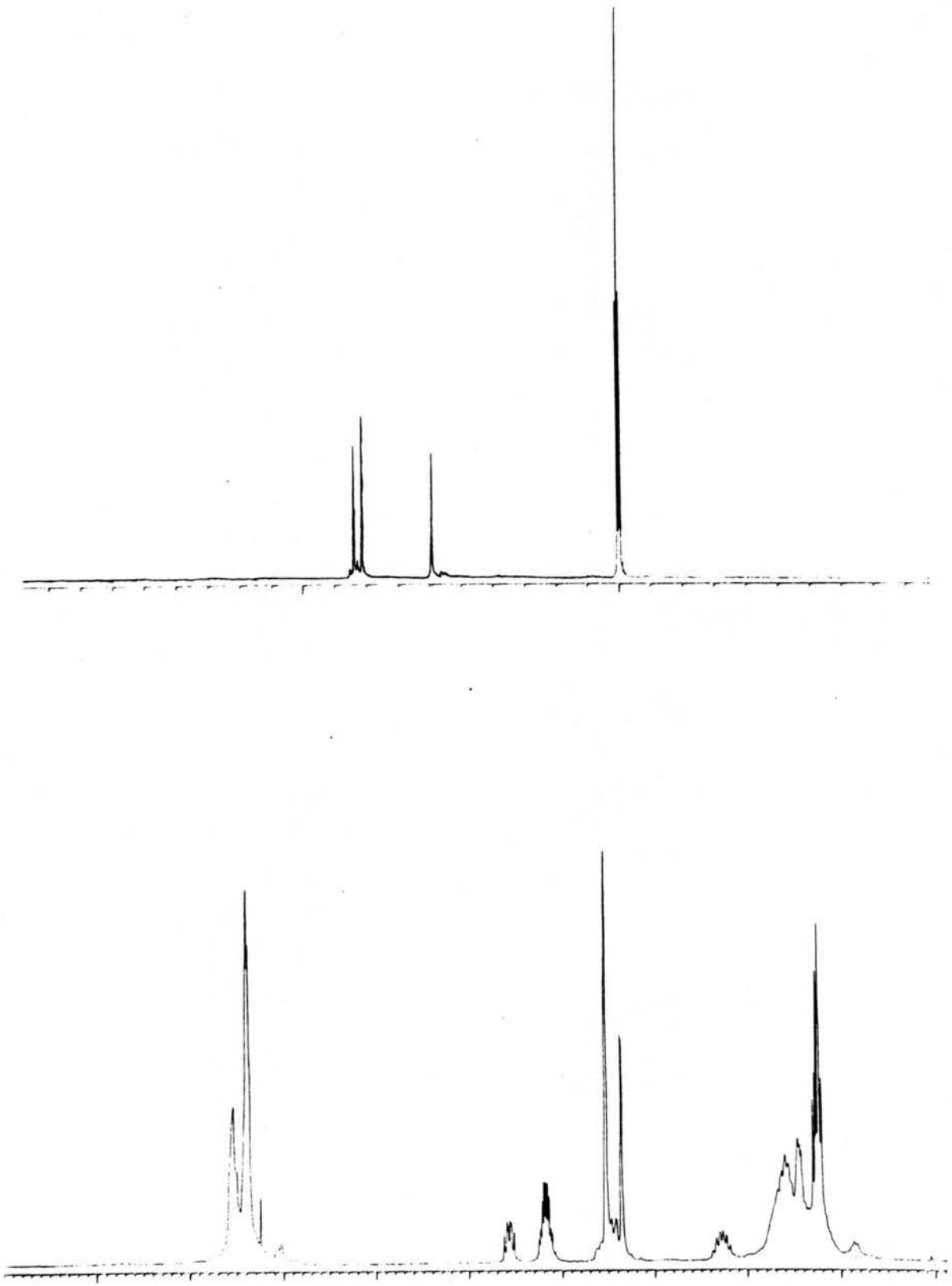


Figure 25a Racemic MPTA Cyclopentylglycine 171 ^{19}F and ^{1}H NMR

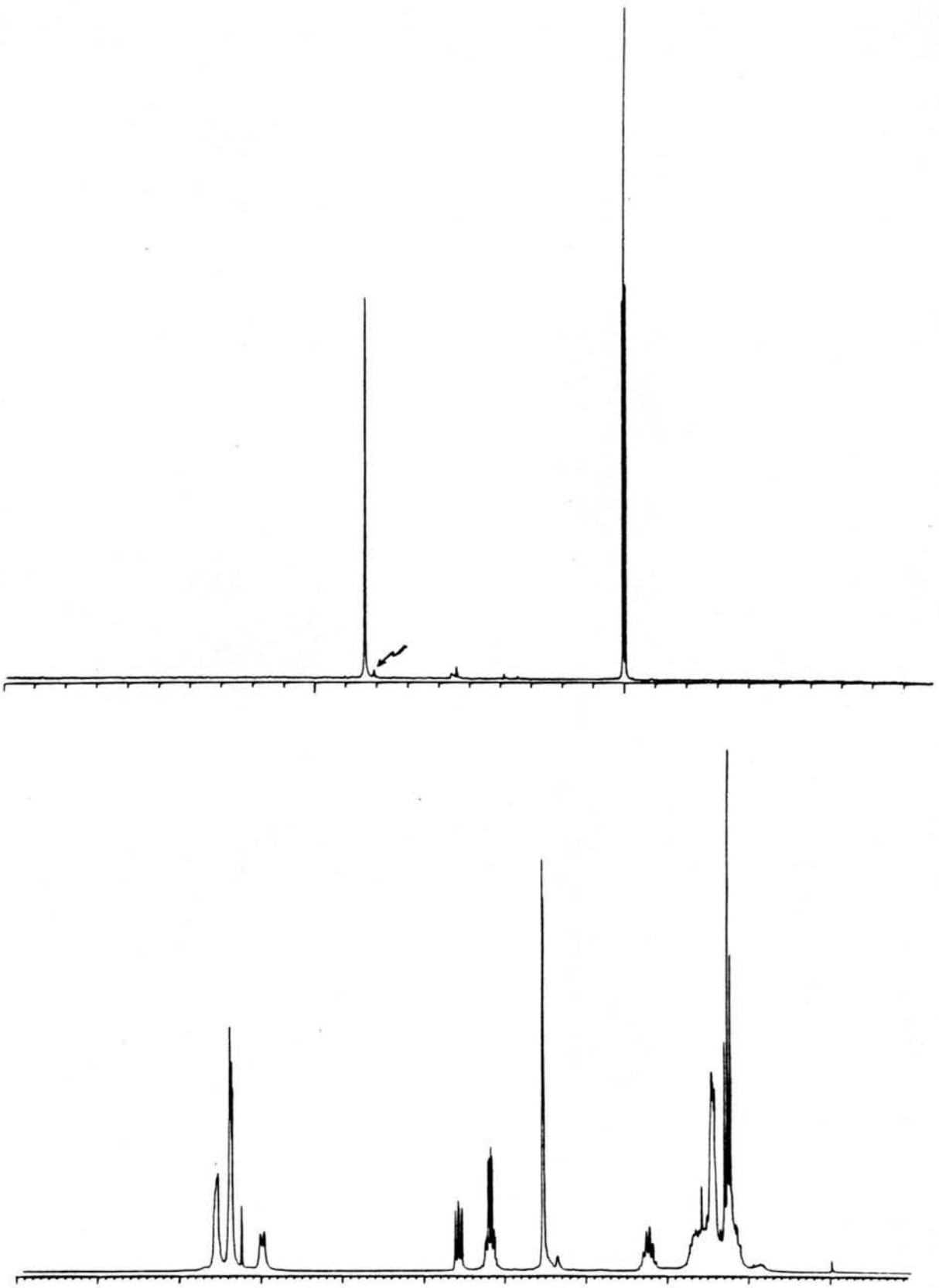


Figure 25b (-)-MPTA (Synthetic) Cyclopentylglycine **171** ^{19}F and ^{1}H NMR

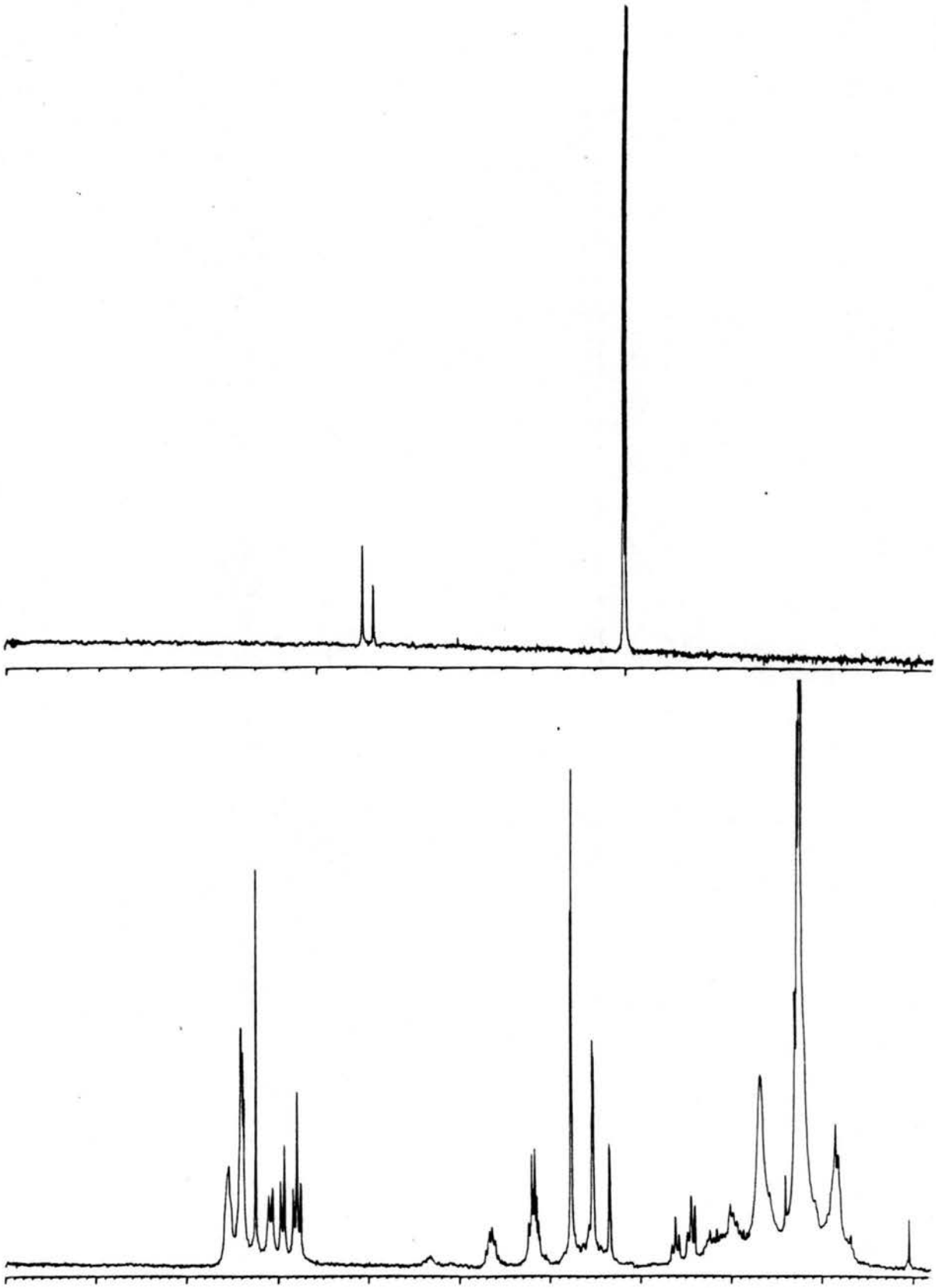


Figure 26a **Racemic MPTA 4-Methoxyhomophenylalanine 191 ^{19}F and ^{1}H NMR**

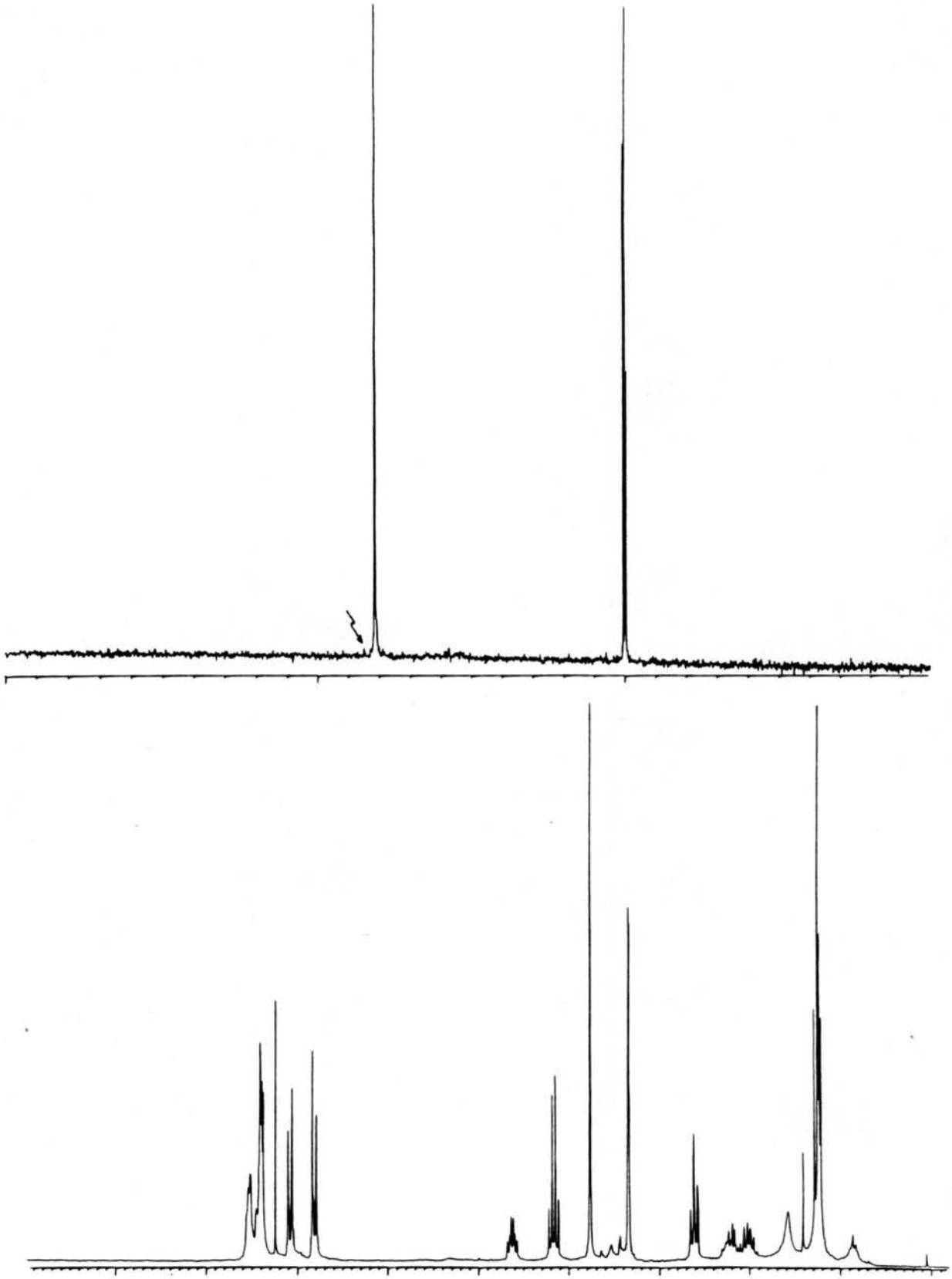


Figure 26b (+)-MPTA (Synthetic) 4-Methoxyhomophenylalanine **191** ^{19}F and ^{1}H NMR

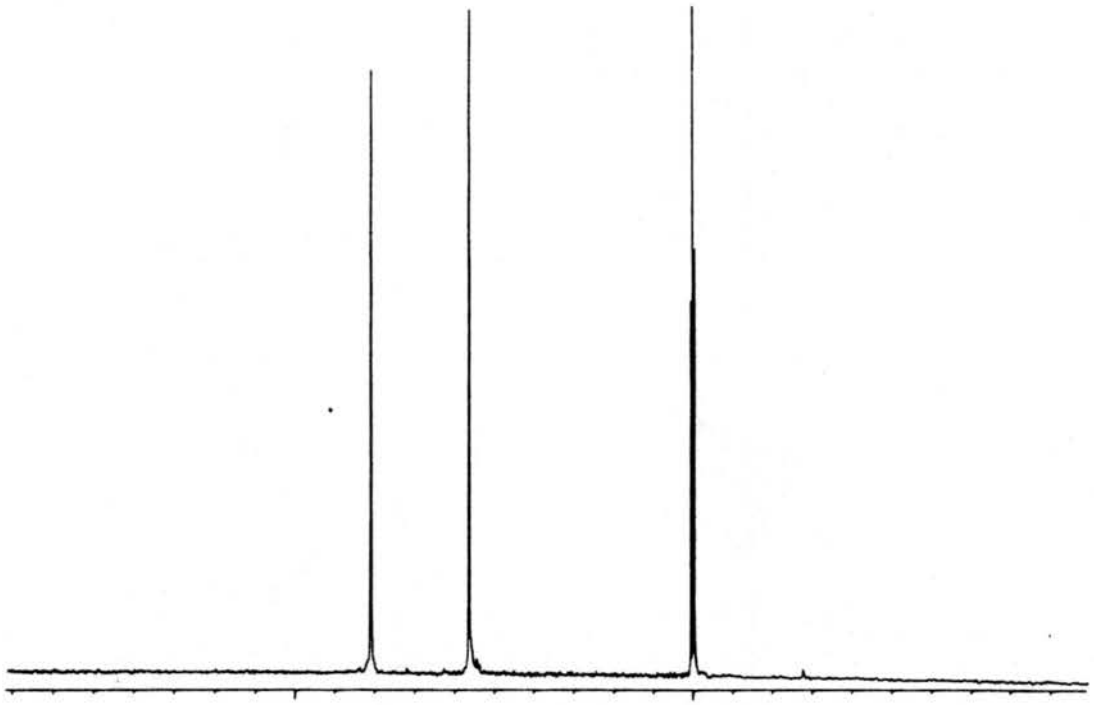


Figure 27a (+)-MPTA Authentic **208**.

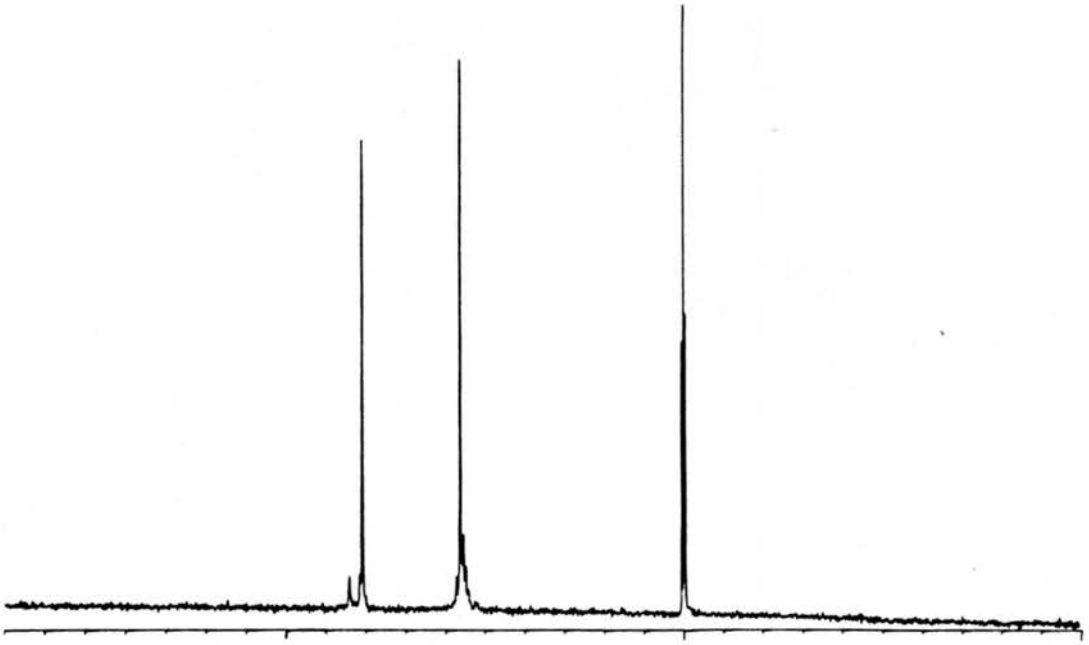


Figure 27b (+)-MPTA Synthetic **208**.

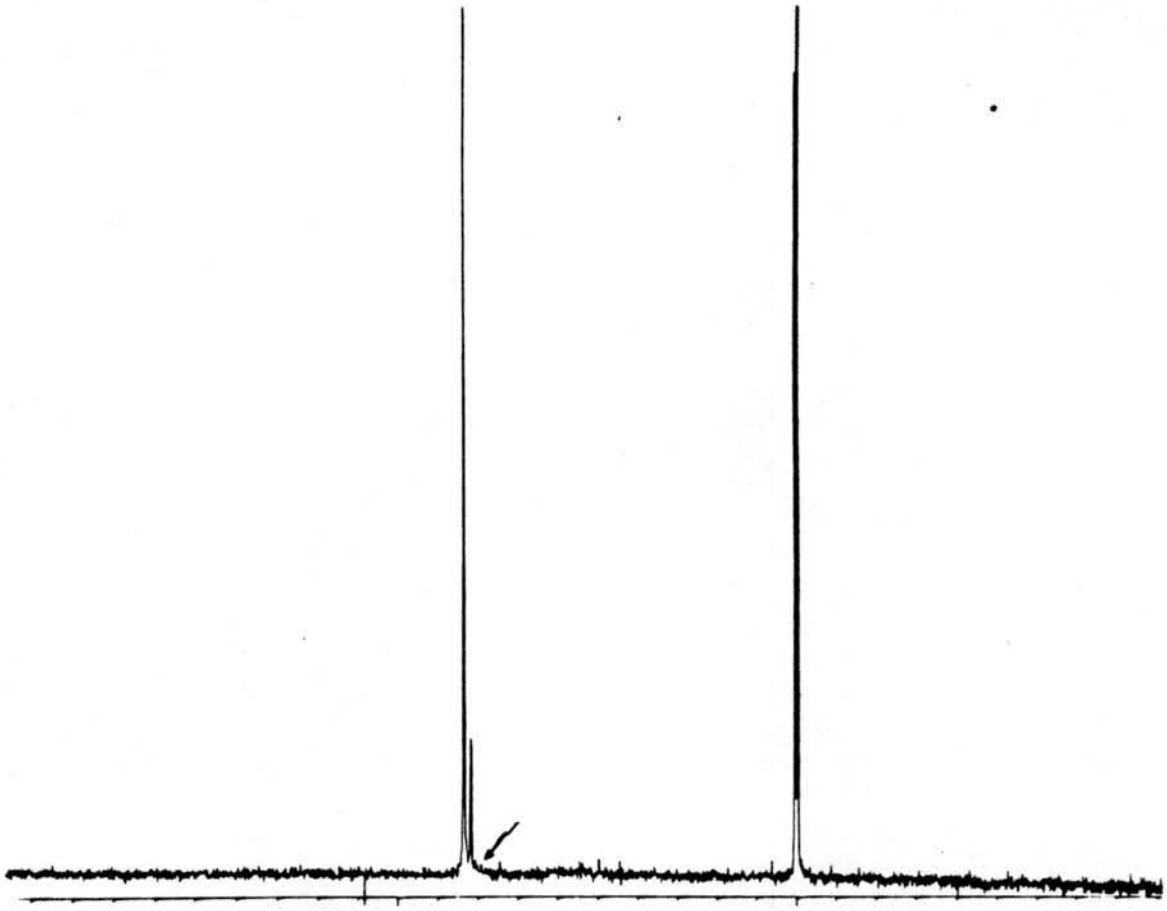


Figure 28a (+)-MPTA (Synthetic) Diethylaspartate Acid **139** obtained from synthetic β-Carboxyaspartic Acid **213**.

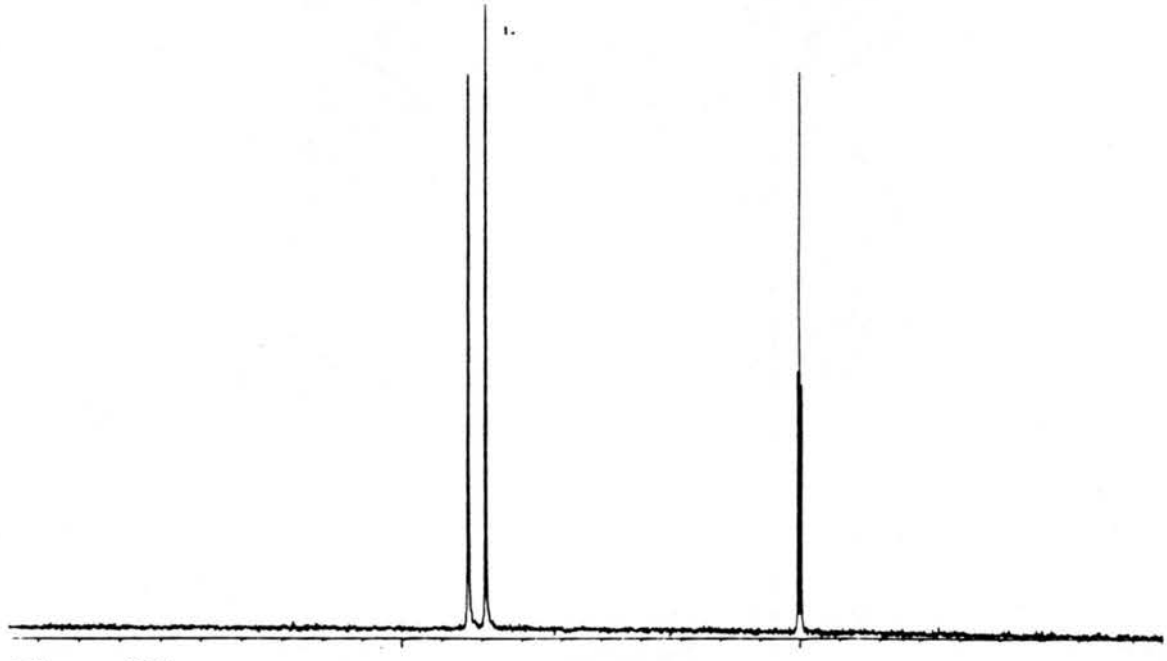


Figure 28b Racemic MPTA Diethylaspartate **139**

CHAPTER V

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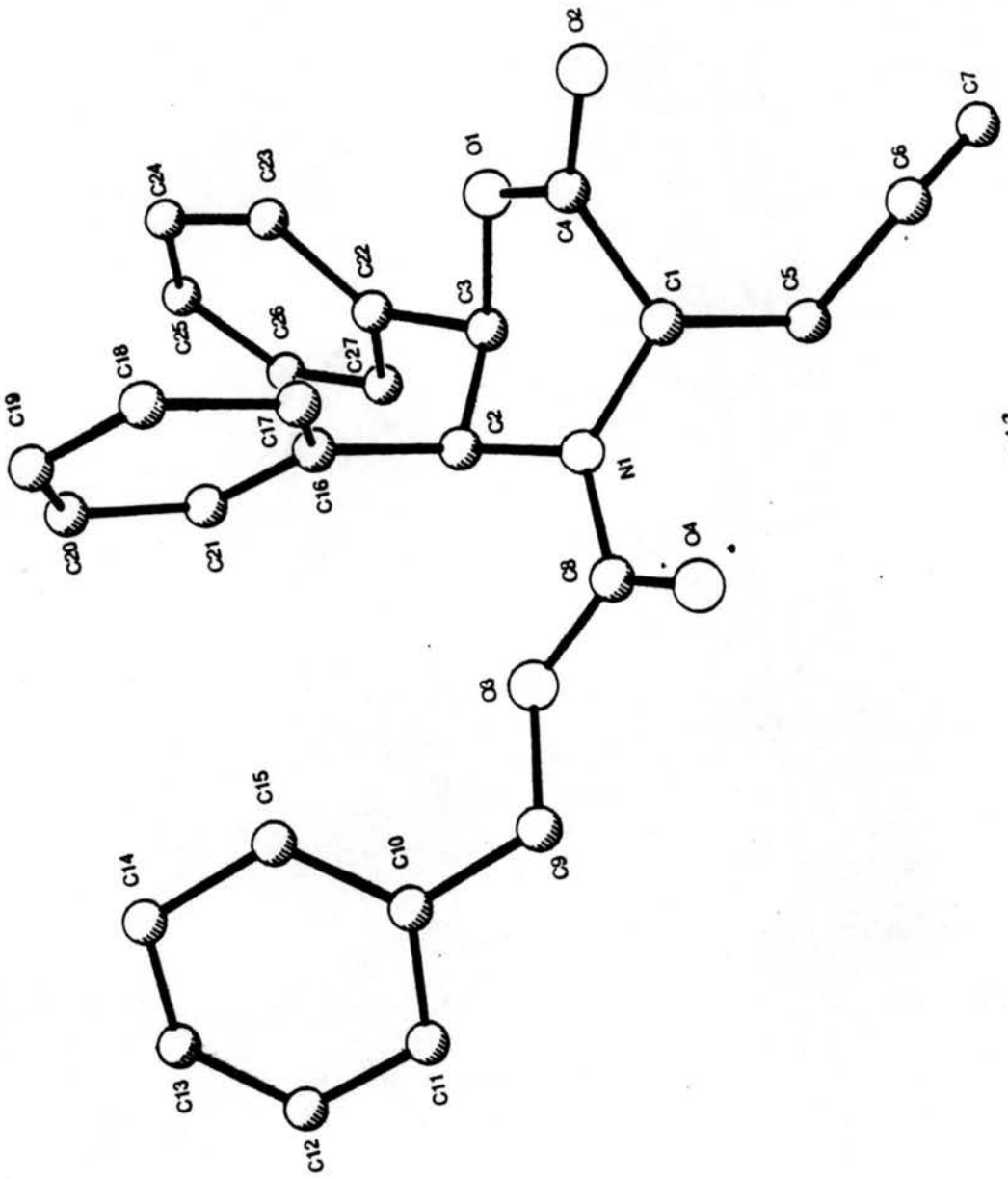
APPENDIX I

X-RAY ANALYSIS DATA FOR **143**


O2
C7
O1
C6
C24
C23
C4
C22
C5
C1
C3
C25
C26
C27
C18
C2
C19
C17
N1
C16
C20
C21
O4
O8
O3
C15
C14
C10
O9
C13
C11
C12

143

TABLE SI. Atomic coordinates ($x10^4$) and thermal parameters ($Å^2 x10^3$)[a] for $C_{27}H_{25}NO_4$

atom	x	y	z	U_{iso}[b]
N1	1521(2)	5362(4)	1395(3)	59(5)
O1	2186(2)	2911(4)	1866(2)	75(5)
O2	1249(2)	2017(4)	1426(2)	87(6)
O3	1290(2)	7322(4)	850(2)	69(5)
O4	537(2)	6551(4)	798(2)	84(5)
C1	1318(3)	4309(5)	1567(3)	65(7)
C2	2046(3)	5148(5)	1441(3)	58(6)
C3	2592(3)	4090(6)	2114(4)	64(7)
C4	1565(3)	2995(5)	1598(3)	70(7)
C5	1640(4)	4556(6)	2419(4)	95(11)
C6	1330(4)	3694(7)	2550(4)	123(11)
C7	1683(5)	3151(7)	3208(5)	180(20)
C8	1065(3)	6430(5)	993(3)	69(7)
C9	784(3)	8405(6)	301(3)	80(7)
C10	978(3)	8991(5)	-45(3)	69(7)
C11	1193(3)	10257(6)	108(4)	106(8)
C12	1370(4)	10773(8)	-223(5)	149(11)
C13	1339(4)	9972(8)	-675(5)	170(14)
C14	1137(4)	8733(8)	-820(5)	151(16)
C15	949(3)	8230(6)	-506(4)	103(11)
C16	1642(3)	4894(5)	553(3)	57(6)
C17	930(3)	4381(5)	-126(3)	70(6)
C18	579(3)	4194(6)	-929(4)	91(8)
C19	922(3)	4536(6)	-1081(4)	93(9)
C20	1633(4)	5044(6)	-407(4)	85(9)
C21	1998(3)	5238(5)	403(3)	68(7)
C22	3155(3)	3765(6)	2215(3)	62(7)
C23	3036(3)	2768(6)	1750(4)	80(8)
C24	3542(3)	2532(6)	1815(4)	96(10)
C25	4162(3)	3296(7)	2335(4)	90(9)
C26	4286(3)	4292(7)	2791(4)	92(9)
C27	3785(3)	4518(6)	2734(3)	79(7)

(a) Estimated standard deviations in the least significant digits are given in parentheses.

(b) Equivalent isotropic U for anisotropic atoms is defined as one third of the trace of the orthogonalized U_{ij} tensor.

TABLE SII. Bond lengths (Å)[a] for $C_{27}H_{25}NO_4$

N1-C1	1.463(11)	N1-C2	1.467(12)
N1-C8	1.367(7)	O1-C3	1.452(8)
O1-C4	1.346(11)	O2-C4	1.193(8)
O3-C8	1.338(10)	O3-C9	1.449(6)
O4-C8	1.201(11)	C1-C4	1.511(9)
C1-C5	1.537(14)	C2-C3	1.522(7)
C2-C16	1.510(10)	C3-C22	1.492(14)
C5-C6	1.485(17)	C6-C7	1.191(14)
C9-C10	1.498(14)	C10-C11	1.367(8)
C10-C15	1.355(14)	C11-C12	1.395(18)
C12-C13	1.356(18)	C13-C14	1.333(12)
C14-C15	1.378(20)	C16-C17	1.371(6)
C16-C21	1.412(14)	C17-C18	1.377(12)
C18-C19	1.379(17)	C19-C20	1.367(8)
C20-C21	1.376(12)	C22-C23	1.382(11)
C22-C27	1.369(8)	C23-C24	1.379(17)
C24-C25	1.360(9)	C25-C26	1.362(13)
C26-C27	1.379(16)		

(a) Estimated standard deviations in the least significant digits are given in parentheses.

TABLE SIII. Bond angles (deg)[a] for $C_{27}H_{25}NO_4$

C1-N1-C2	121.0(5)	C1-N1-C8	115.7(7)
C2-N1-C8	121.4(7)	C3-O1-C4	118.6(5)
C8-O3-C9	116.3(6)	N1-C1-C4	113.0(8)
N1-C1-C5	110.7(5)	C4-C1-C5	110.1(5)
N1-C2-C3	107.5(7)	N1-C2-C16	112.3(4)
C3-C2-C16	114.8(6)	O1-C3-C2	110.4(4)
O1-C3-C22	107.6(6)	C2-C3-C22	112.9(8)
O1-C4-O2	118.3(6)	O1-C4-C1	119.0(6)
O2-C4-C1	122.7(8)	C1-C5-C6	114.3(5)
C5-C6-C7	126.2(9)	N1-C8-O3	111.0(7)
N1-C8-O4	124.4(7)	O3-C8-O4	124.6(5)
O3-C9-C10	107.3(7)	C9-C10-C11	121.7(8)
C9-C10-C15	118.6(6)	C11-C10-C15	119.7(10)
C10-C11-C12	120.3(9)	C11-C12-C13	117.9(8)
C12-C13-C14	122.3(14)	C13-C14-C15	119.8(13)
C10-C15-C14	120.0(7)	C2-C16-C17	122.6(8)
C2-C16-C21	119.1(5)	C17-C16-C21	118.3(7)
C16-C17-C18	120.5(9)	C17-C18-C19	121.5(6)
C18-C19-C20	118.4(9)	C19-C20-C21	121.3(11)
C16-C21-C20	120.0(6)	C3-C22-C23	121.7(6)
C3-C22-C27	119.9(7)	C23-C22-C27	118.2(9)
C22-C23-C24	120.8(6)	C23-C24-C25	119.7(8)
C24-C25-C26	120.4(11)	C25-C26-C27	119.8(7)
C22-C27-C26	121.0(7)		

(a) Estimated standard deviations in the least significant digits are given in parentheses.

TABLE SIV. Anisotropic thermal parameters ($Å^2 \times 10^3$) [a,b] for $C_{27}H_{25}NO_4$

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	55(3)	71(3)	67(3)	5(3)	52(3)	4(2)
O1	73(3)	71(3)	96(3)	10(2)	70(3)	2(2)
O2	102(3)	86(3)	108(3)	-6(2)	92(3)	-18(2)
O3	59(2)	78(3)	78(3)	18(2)	56(2)	18(2)
O4	71(2)	105(3)	107(3)	6(3)	78(3)	10(2)
C1	67(4)	74(4)	74(4)	0(3)	60(3)	-2(3)
C2	44(3)	70(4)	64(4)	5(3)	44(3)	1(3)
C3	53(3)	72(4)	63(4)	2(4)	46(3)	1(4)
C4	69(4)	94(5)	61(4)	1(3)	55(3)	-7(3)
C5	131(6)	98(6)	111(6)	-2(5)	109(5)	-9(5)
C6	149(6)	136(7)	108(6)	16(5)	108(6)	10(5)
C7	334(12)	114(7)	215(9)	31(7)	247(10)	55(8)
C8	57(3)	95(5)	65(4)	-2(3)	51(3)	-0(3)
C9	65(4)	95(5)	73(4)	10(4)	54(4)	25(4)
C10	50(3)	68(4)	59(4)	6(3)	37(3)	11(3)
C11	76(4)	89(5)	65(4)	5(4)	35(4)	3(4)
C12	88(5)	113(7)	123(7)	47(5)	56(5)	-4(5)
C13	119(6)	201(9)	192(8)	133(7)	125(7)	74(6)
C14	202(9)	160(9)	186(8)	101(7)	177(8)	114(7)
C15	143(6)	83(5)	127(6)	30(4)	118(5)	37(4)
C16	49(3)	67(4)	53(3)	0(3)	40(3)	4(3)
C17	44(3)	91(5)	54(4)	-10(3)	34(3)	-6(3)
C18	61(4)	108(6)	66(4)	-11(4)	42(4)	-1(4)
C19	89(5)	123(6)	69(4)	-0(4)	64(4)	20(4)
C20	85(5)	107(6)	83(4)	12(4)	71(4)	20(4)
C21	57(3)	81(4)	63(4)	8(3)	47(3)	9(3)
C22	48(3)	67(4)	61(4)	11(3)	42(3)	11(3)
C23	67(4)	68(5)	100(5)	4(4)	65(4)	5(4)
C24	96(5)	88(5)	124(6)	5(4)	92(5)	19(4)
C25	64(4)	113(6)	107(6)	16(5)	71(4)	16(4)
C26	51(4)	115(7)	81(5)	-5(4)	46(4)	-10(4)
C27	51(4)	103(6)	62(4)	-1(4)	40(3)	0(3)

(a) Estimated standard deviations in the least significant digits are given in parentheses.

(b) The anisotropic thermal parameter exponent takes the form:

$$-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+ \ldots +2hka^*b^*U_{12})$$

TABLE SV. Hydrogen atom coordinates ($x10^4$) and thermal parameters ($Å^2 x10^3$) for $C_{27}H_{25}NO_4$

atom	x	y	z	U_{iso}
H1	777	4298	1086	87
H2	2331	5917	1630	75
H3	2855	4423	2658	82
H5A	1531	5436	2415	126
H5B	2176	4434	2900	126
H6	795	3559	2056	152
H7A	1723	3450	3603	187
H7B	1825	2255	3322	187
H9A	270	8110	-174	98
H9B	850	9036	636	98
H11	1221	10794	443	130
H12	1511	11666	-130	168
H13	1468	10311	-898	191
H14	1121	8194	-1144	181
H15	798	7340	-618	123
H17	675	4148	-40	90
H18	84	3819	-1394	114
H19	667	4423	-1648	112
H20	1884	5264	-500	106
H21	2494	5610	865	86
H23	2596	2235	1377	102
H24	3457	1832	1495	122
H25	4515	3133	2380	110
H26	4723	4834	3152	115
H27	3878	5213	3063	104

Table SVI. Details of the Crystallographic Experiment

Mol Formula: $C_{27}H_{25}NO_4$

Formula wt: 427.5 gr/mol
Crystal system: Monoclinic (C-centered)
Space Group: C 2/c
Lattice Constants:

a:	29.325(11)Å			Volume:	4633 Å^3
b:	10.326(1)Å	β:	142.79(1)°	Z:	8
c:	25.316(7)Å				

Temperature: 20(1)°C
Density (calculated): 1.22 g cm^{-3}
Density (determined): 1.23 g cm^{-3}
Crystal dimensions: 0.1 mm x 0.3 mm x 0.3 mm
Radiation: MoK (alpha) (lambda: 0.71073A)
Monochromator: graphite
μ: 0.9 cm^{-1}
Scan Type: Theta/two theta
Geometry: Bisecting
Two theta range: 3.5 to 50.0 deg.
Scan speed: variable, 4 to 29 deg/min^{-1}
Index restrictions: $-35 \leq h \leq 35$ $-13 \leq k \leq 0$ $-31 \leq l \leq 0$
Total number of reflections: 3582
No. of unique, observed ref.: 1514
Observed criterion: $F > 2.5$ sigma F
Final data to parameter ratio: 5.2

R: .0711
R_w: .0637
GOF: 1.31

APPENDIX II

REPRINTS

J. Am. Chem. Soc. 1986, *108*, 1103–1104

Electrophilic Glycinates: New and Versatile Templates for Asymmetric Amino Acid Synthesis

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Received September 3, 1985

The number of naturally occurring α-amino acids has grown substantially beyond the roughly 20 amino acids normally found in proteins; over 500 are now known.[1] In addition, there has been a tremendous surge of interest in the asymmetric preparation of relatively inaccessible unnatural amino acids whose potential biological properties and general synthetic utility are just beginning to be realized. Of the methods presently available, there is a general lack of access to optically pure α-monosubstituted α-amino acids and derivatives in both the D and L configuration. Several groups have recently reported the asymmetric alkylation of amino acid derived enolates[2] to furnish α-disubstituted amino acids and, in one approach,[3] the enolates of optically active lactim ethers of diketopiperazines furnishes the α-monosubstituted α-amino acids. The more classical approaches involving the asymmetric hydrogenation of prochiral dehydro amino acid derivatives[4] or hydrogenation of chiral dehydro amino acid derivatives[5] suffer from the range of substitution accessible on the α-"R" group and the variations in the percent asymmetric synthesis (i.e., % ee). In this preliminary account, we wish to report a new and general method for preparing both D- and L-α-monosubstituted α-amino acids via C–C bond-forming reactions on *electrophilic* glycinates[6] that is complementary to the existing enolate-based methodologies.

According to Tischler et al.,[7] D,L-*erythro*-α,β-diphenyl-β-hydroxyethylamine is efficiently resolved on large scale through the agency of the derived glutamate salts to furnish both optically pure antipodes of **1**.[7] Sequential N-alkylation with ethyl bromoacetate (Et_3N, THF, 25 °C), Schotten–Baumann acylation (BnOCOCl, $NaHCO_3$(aq), CH_2Cl_2), and cyclization (catalytic *p*-TsOH, PhH, reflux) furnished the optically pure lactone **2** (mp 200 °C; $[\alpha]^{25}_D$ −66.7°, *c* 0.815, CH_2Cl_2) in 65% overall yield from **1**. Bromination of **2** was realized by treatment with 1 equiv of NBS in warm CCl_4 to afford after filtration of insoluble succinimide the bromide **3** as an amorphous white powder. The bromide **3** is produced in essentially quantitative yield[8] (crude, by ^1H NMR) but decomposes upon exposure to silica gel chromatography. The bromide can be stored indefinitely as a solid in the dark and is directly used for the subsequent C–C coupling reactions as described in Scheme I.

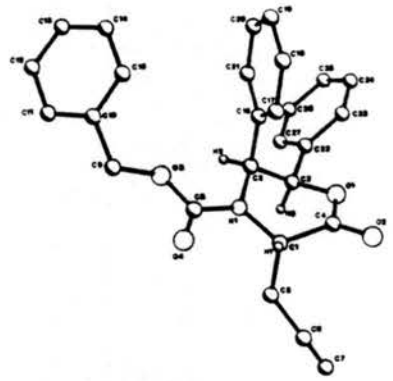
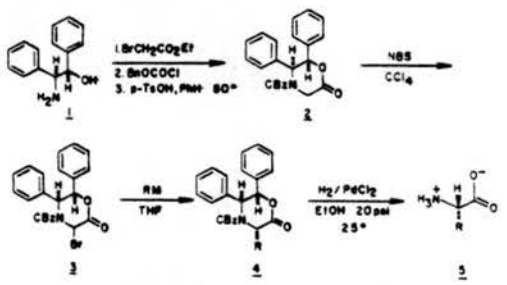


Figure 1. Molecular Structure of **4** (R = $CH_2CH{=}CH_2$). Atoms are shown as spheres of fixed, arbitrary radius.

Scheme I



The bromoglycinate **3** is a very reactive electrophile toward a variety of carbon nucleophiles; those described herein constitute a superficial initial screening and are representative of many possible extensions and variations. A typical procedure is described below for the preparation of β-ethylaspartate.

To a stirred solution of lactone **2** (0.2 g, 0.51 mmol) in refluxing CCl_4 (60 mL) was added NBS (0.11 g, 0.62 mmol). The mixture was allowed to reflux for 35 min, cooled to 0 °C, filtered, and evaporated to afford the bromide **3** as a white powder which was used directly for the next step. The bromide **3** (0.108 g, 0.23 mmol) was dissolved in THF (4 mL) and the (*tert*-butyldimethylsilyl)ketene acetal of ethyl acetate (0.11 mL, 0.58 mmol) was added followed by a solution of anhydrous $ZnCl_2$ (1.5 mL of a 0.17 N solution in THF) at 25 °C. The reaction was allowed to stir for 1 h at 25 °C, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (3:1, hexanes/EtOAc) to afford 78.6 mg (71%) of the lactone **4** (R = CH_2CO_2Et). This material was dissolved in absolute EtOH (3 mL) plus THF (1 mL), $PdCl_2$ (13.2 mg) was added, and the system was flushed with H_2 and hydrogenated at 20 psi for 24 h at 25 °C. Filtration of the catalyst through Celite, concentration, and addition of Et_2O precipitates the zwitterionic amino acid (**5**, R = CH_2CO_2Et) (25 mg, quantitative) as a white powder. The percent asymmetric synthesis (% ee) on this and the other amino acids listed in the table was determined by acylating[9] the crude amino acid with (+)-α-methoxy-α-(tri-

(1) For a review, see: Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(2) (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337.

(3) Schollkopf, U. *Tetrahedron* **1983**, *39*, 2085 and references cited therein. See also: Belokon, Y. N.; Zel'tzer, I. E.; Bakhmutov, V. I.; Saporovskaya, M. B.; Ryzhov, M. G.; Yanovsky, A. I.; Struchkov, Y. T.; Belikov, V. M. *Ibid.* **1983**, *105*, 2010.

(4) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; American Chemical Society: Washington, DC, 1976.

(5) (a) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476. (b) See also: Vigneron, J. P.; Kagan, H.; Horeau, A. *Tetrahedron Lett.* **1968**, 5681.

(6) The present concept originated in the synthetic work related to bicyclomycin: Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P. *J. Am. Chem. Soc.* **1985**, *107*, 3246. Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *Ibid.* **1985**, *107*, 3253 and references cited therein.

(7) Weijlard, J.; Pfister, K.; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216. For simplicity only the D-erythro series is illustrated; data for both series are in the Supplementary material.

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1104

Table I

RM	reactn condtns	yield 4	amino acid 5[a]	% ee
	1.2$ZnCl_2$, THF, 25 °C, 1 h	71%	D-β-ethylaspartate	96.6
	1.2$ZnCl_2$, THF, 25 °C	54%	L-homophenylalanine	96.9
	2$ZnCl_2$, THF, 25 °C, 3 days	68%	L-norvaline, L-allylglycine[b]	98.3
MeZnCl	THF, 25 °C, 1 h	46%	L-alanine	96.8
$Me_2CuCNLi_2$	THF, −78 °C, 30 min	28%		
$Bu_2CuCNLi_2$	THF, −78 °C 30 min	48%	L-norleucine	99.5

[a] The conversions of 4 → 5 proceed in essentially quantitative yields in all cases. [b] The conversion of 4 → 5 is carried out with Li/NH_3/EtOH.

fluoromethyl)phenylacetyl chloride and examination of the crude mixture by ^{19}F and ^1H NMR and comparison to the authentic diastereomers prepared from the racemic amino acids. We have also found that for substrates containing unsaturated functionality, such as the allyl case, the conversion of 4 → 5 can be performed by a dissolving metal reduction ($Li/NH_3(l)$/EtOH) and thus precludes the saturation of the olefin (see Table I for allylglycine).

The substrate 3 is best suited for coupling with "neutral" carbon nucleophiles, such as the silyl enol ethers; the diminished yields for the more basic organometallic reagents is due to competing reduction of 3 → 2. Examination of the crude coupling reaction mixtures (3 → 4) provided no evidence for the formation of alternative diastereoisomers (4); the diastereoselectivity of the nucleophilic additions to 3 in the cases studied is, therefore, excellent.

A single-crystal X-ray analysis of 4 (R = $CH_2CH{=}CH_2$) has been performed[10] as shown in Figure 1. The structure clearly shows that the nucleophile has attacked 3 or putative iminium species from the least hindered face to furnish, from the D series (of 1) after hydrogenation, L-norvaline as expected. This trend is followed for most of the carbon nucleophiles examined thus far. The notable and curious exception, however, was found in the preparation of β-ethyl aspartate. From the D-series lactone, D-β-ethylaspartate is produced in >96% ee which indicates that the resulting lactone 4 (R = CH_2CO_2Et) must possess the all-syn configuration. The molecular structure of 4 (R = $CH_2CH{=}CH_2$), shown in Figure 1, shows that the tetrahydrooxazinone has adopted a twist-boat conformation that situates the phenyl ring at C-2 (X-ray numbering) in a pseudoaxial orientation. It is reasonable to assume that a reactive intermediate derived from 3 would also have a similar conformation, since that shown avoids A strain as well as 1,3-diaxial interactions that would be experienced in alternative conformations.

It must be concluded that the *tert*-butyldimethylsilyl enol ether of ethyl acetate is selectively coupling from the sterically more encumbered face or that epimerization of an initially formed anti isomer to the syn isomer occurs under the reaction conditions. Efforts are under way to elucidate the factors governing this anomalous, yet highly selective, coupling reaction.

In summary, a new and potentially highly versatile method[11,12] for the preparation of natural and unnatural α-amino acids in both the D and L configuration has been developed. The percent asymmetric synthesis (% ee) for the cases studied herein are uniformly high, and the entire sequence beginning with benzoin[7] proceeds with efficiency, requiring only a single chromatographic isolation at the stage of 4. Efforts to further expand the scope and utility of this methodology are presently under active investigation in these laboratories.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial support of this work and an NIH Research Career Development Award (to R.M.W.). We also wish to express thanks to Professor Dave Evans for helpful discussions and communicating their results to us in a related system prior to publication.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of 4; ^1H NMR spectra of amino acids obtained without purification from the hydrogenation of 4, and listing of spectroscopic and analytical data for all new compounds (14 pages). Ordering information is given on any current masthead page.

(8) It was not possible to assign the relative configuration of the crude bromide due to slow conformational exchange on the ^1H NMR time scale.

(9) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(10) Data were collected on an Nicolet R3m X-ray diffractometer. All crystallographic computations were carried out using the SHELXTL program library (written by G. M. Sheldrick and supplied by Nicolet XRD for the Data General Eclipse S/140 computer in the crystallographic laboratory at Colorado State University). Lattice constants a = 29.325 (11) Å; b = 10.326 (1) Å; c = 25.316 (7) Å, β = 142.79 (1)°, monoclinic (C centered). R = 0.0711, R_w = 0.0637, GOF = 1.31.

(11) An example of racemic amino acid synthesis via electrophilic glycinates has recently appeared in addition to that mentioned in ref 6; see: O'Donnell, M. J.; Falmagne, J. B. *Tetrahedron Lett.* **1985**, *26*, 699.

(12) Various attempts at generating the enolate anions of 2 and 4 followed by electrophilic quenching resulted in decomposition only.

Reprinted from The Journal of Organic Chemistry, 1986, 51, 5021

Asymmetric Synthesis of (*R*)- and (*S*)-[2-$^2H_1$]Glycine

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Received May 19, 1986

Chiral glycine[1] has become an increasingly important substance for the study of numerous biochemical reactions and serves as a starting material for stereospecific conversions into other important, labeled compounds such as chiral acetic[2] and chiral glycolic[3] acids. A number of syntheses of chiral glycine have been reported[1] that involve one or two enzyme-mediated transformations or involve unambiguous chemical syntheses from chiral, nonracemic starting materials such as other amino acids or sugars. The somewhat capricious nature of the enzyme-mediated syntheses and the tediousness of the multistep chemical syntheses make this deceptively simple molecule a challenging and important target for efficient asymmetric synthesis. We recently reported[4] a new asymmetric synthesis of α-amino acids based on the chiral electrophilic glycinate **2**. In this paper, we further demonstrate the utility of this method by reporting an efficient two-step stereospecific synthesis of (*R*)- and (*S*)-[2-$^2H_1$]glycine from the readily available[4] glycinates **1**.

Bromination of (−)-5(*S*),6(*R*)-**1** as previously described[4] furnishes the bromide **2** as a white solid (Scheme I). Reduction of **2** with D_2 at 40 psi in the presence of catalytic $PdCl_2$ in D_2O/THF at 25 °C for 40 h directly furnishes (*S*)-[2-$^2H_1$]glycine in 51–54% yield. The isotopic purity of this material at C-2 was determined to be at least 84–90% and the optical purity (% ee) was established at 77–82% according to the procedure of Armarego et al.[5] Specifically, acylation of **3** with (−)-camphanyl chloride (**4**) furnished the amides (**5a,b**, which were examined by ^1H NMR (Scheme II). Comparison of the resonances near δ 4 with that of the amides **5c** prepared from racemic [2-$^2H_1$]glycine obtained from racemic **1** rigorously established the stereochemical purities of (*S*)- and (*R*)-**3**. The isotopic purity was similarly obtained by comparing the ^1H NMR spectra of the camphanyl amide **5d** of glycine with those of the chiral glycine derivative (Figure 1).

The stereochemical outcome of the reduction clearly indicates that the C–D bond is formed from the sterically less encumbered face of the presumed putative imine **6** (Scheme III).

It is noteworthy that reduction of (−)-5(*S*),6(*R*)-**2** with Bu_3SnD followed by hydrogenolysis (H_2/Pd/C) produced (*R*)-**3**, in 60% ee (ie., the *reverse* stereochemical outcome from the hydrogenolysis).

Similarly, the conversion of (+)-5(*R*),6(*S*)-**1** into (*R*)-**3** proceeds with equal efficiency. Although the optical purity of the chiral glycine obtained by the present method is slightly lower than that reported previously,[1,5] the relatively high overall chemical yield and experimental simplicity of this synthesis render this contribution a practical alternative to the significantly more laborious syntheses.[1] Furthermore, since the isotopic atom is introduced in the very last transformation, this methodology should be particularly appealing to those interested in synthesizing [2-$^3H_1$]glycine.

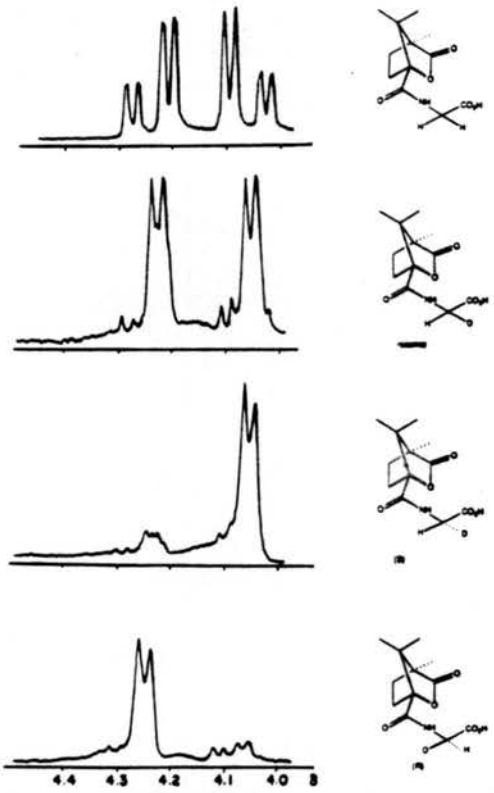

Figure 1. ^1H NMR spectra of camphanyl amides at 270 MHz between δ 4.0 and 4.4: (a) **5d**; (b) **5c**; (c) **5a**; (d) **5b**.

Experimental Section

(*S*)-[2-$^2H_1$]Glycine. The bromide (−)-5(*S*),6(*R*)-**2** (0.274 mmol, 1 equiv) is dissolved in dry THF (5 mL) and D_2O (1 mL) and placed in a pressure bottle that had been base washed with NaOD/D_2O. To this solution was added $PdCl_2$ (14.6 mg, 0.082 mmol, 0.3 equiv) and the vessel was charged with D_2 at 40 psi.

† Fellow of the Alfred P. Sloan Foundation, 1986–1988. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee, 1986–1988.

(1) Ohrui, H.; Misawa, T.; Meguro, H. *J. Org. Chem.* **1985**, *50*, 3007 and references cited therein.
(2) Kajiwara, M.; Lee, S. F.; Scott, I. *J. Chem. Soc. Chem. Commun.* **1978**, 967.
(3) Retey, J.; Robinson, J. A. *Stereospecificity in Organic Chemistry and Enzymology*; Verlag Chemie: Weinheim, 1982; Vol. 13, p 161.
(4) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.
(5) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans 1* **1976**, 2229.

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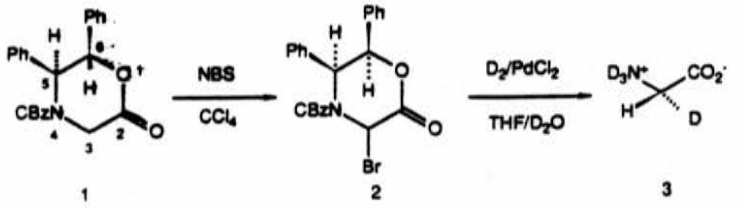
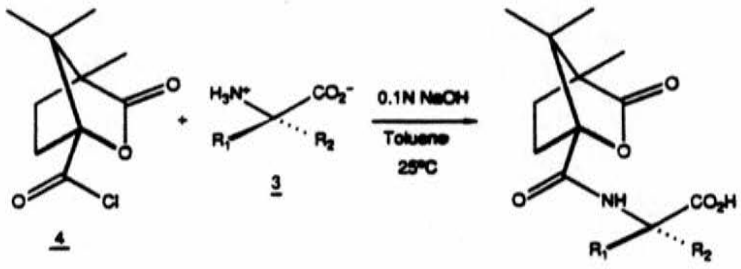
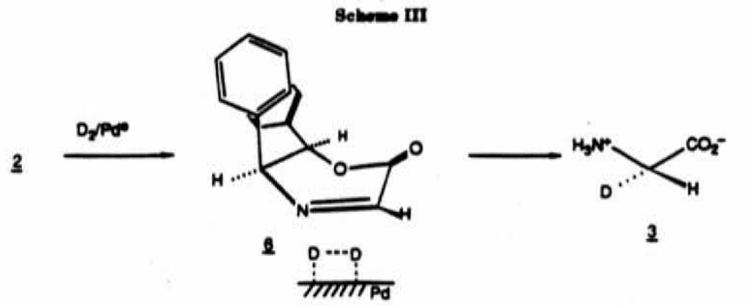
Scheme I



Scheme II



Scheme III



The mixture was allowed to stir for 40 h at 25 °C, and the pressure was reduced to 1 atm and the mixture purged with N_2. The mixture was filtered through a pad of Celite, evaporated to an oily residue, and triturated with CH_2Cl_2, THF, and Et_2O, leaving the insoluble *crystalline* amino acid [23.6 mg (54%)] as its hydrohalogen salt. The free amino acid was obtained by dissolution of the hydrohalogen salt in H_2O (57.5 mg) and eluting the solution with 1 N NH_4OH through an ion-exchange resin (Dowex 50W-X8, 20–50 mesh, in H^+ form after washing with 1 N NaOH and 10% H_2SO_4). Recrystallization from MeOH yielded white crystals: 22.5 mg; mp 235.5 °C dec (lit.[5] mp 234 °C dec); 82% isolated yield (from the amino acid salt); ^1H NMR (270 MHz) δ 3.65 (t).

Determination of Optical Purity (Amides 5). The crude amino acid (as the hydrohalogen salt obtained from the hydrogenolysis (6.9 mg, 0.044 mmol, 1.0 equiv) in 0.1 N NaOH solution (2.2 mL, 0.218 mmol, 5.0 equiv) was added to a stirred solution of (−)-camphanyl chloride (4; 18.8 mg, 0.087 mmol, 2.0 equiv) in toluene (1 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 4.5 h at 25 °C. The mixture was thoroughly extracted with $CHCl_3$ (discarded), the aqueous phase was acidified with 1 N HCl, and the resultant solution was thoroughly extracted with CH_2Cl_2. The combined extracts were evaporated and directly analysed by ^1H NMR ($CDCl_3$, 270 MHz). The spectroscopic properties of the amides 5 so obtained were identical with those previously reported.[5] The region between δ 4 and 5 was utilized for the determination of optical and isotopic purity as illustrated in Figure 1.[6]

Acknowledgment. We thank the National Science Foundation for their generous support of this work.

Registry No. (−)-(5*S*,6*R*)-1, 100516-54-9; (+)-(5*R*,6*S*)-1, 105228-46-4; 2, 100670-94-3; (*S*)-3, 62061-66-9; (*R*)-3, 62061-53-4; (*S*)-3·HBr, 105183-10-6; 4, 39637-74-6; 5a, 88315-13-3; 5b, 88291-60-5; 5d, 62061-66-9.

(6) The percent ee and isotopic purities were obtained by calculation from the ^1H NMR integrals. Since the peaks from the protio species 5d overlap with portions of the peaks from 5a and 5b, the resolved portion of the signals at δ 4.3 was accurately integrated and the calculated remaining signals that were not resolved were substracted from the portion of the spectrum between δ 4.0 and 4.1 (for 5a, for example). Each spectrum was recorded at least twice, and the integrals for each spectrum were measured at least twice, and averaged.