DISSERTATION

THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA GLYCINE ENOLATES

Submitted by

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In partial fulfillment of the requirements

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY MYEONG-NYEO IM ENTITLED "THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA GLYCINE ENOLATES" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Adviser

Department Head

ABSTRACT OF DISSERTATION

THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA GLYCINE ENOLATES

The enolates derived from the optically active D-erythro-4-(*tert*-butyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (**166a**) and D- and L-erythro-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-ones (**167a/b**) efficiently couple with alkyl halides to afford the corresponding *anti*-α-monosubstituted oxazinones. The enolate alkylation of the α-monosubstituted oxazinones provides the corresponding α-disubstituted oxazinones. Dissolving-metal reduction of the homologated oxazinones allows the direct preparation of t-BOC protected α-amino acids. In the case of dissolving metal-reducible functionality, hydrogenation over a Pd° catalyst furnishes the zwitterionic amino acids. By employing this protocol the syntheses of complex amino acids such as 2-(*tert*-butyloxycarbonyl)amino-6-(*p*-methoxybenzyl)thionohexanoic acid and 2,6-diamino-6-hydroxymethylpimelic acid are discussed.

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DEDICATION

This dissertation is dedicated to the memory of my parents. Their priceless love, support and encouragement made this work possible and worthwhile. The news that they had died during my stay in U.S.A. amazed me and made me so sad. I will never forget their love.

ACKNOWLEDGEMENTS

There are a number of people whose assistance and guidance made my graduate experience invaluable. Without their contributions this dissertation would not be nearly as impressive.

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A very special thanks to Michelle Pinkerton; she did a wonderful job typing and arranging this thesis. She was so kind and friendly to me.

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TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION 1

A. Background 1

B. Synthesis of α-Amino Acids *via* Nucleophilic Glycine Equivalents 3

C. Erythro-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-ones as Electrophilic Glycinates 34

CHAPTER 2

ERYTHRO-5,6-DIPHENYL-2,3,5,6-TETRAHYDRO-4H-1,4-OXAZIN-2-ONES AS NUCLEOPHILIC GLYCINATES 44

A. Synthesis of α-Amino Acids 44

B. Synthesis of α-Disubstituted Amino Acids 58

CHAPTER 3

SYNTHESIS OF 2-(*tert*-BUTYLOXYCARBONYL)AMINO-6-(*p*-METHOXYBENZYL)THIONOHEXANOIC ACID 72

CHAPTER 4

SYNTHETIC APPROACH TO N-(2,6-DIAMINO-6-HYDROXYMETHYLPIMELYL)-L-ALANINE 77

CHAPTER 5

EXPERIMENTAL SECTION 97

A. General Information 97

B. Chromatography 98

C. Reagents and Solvents 98

D. General Experimental Considerations 98

REFERENCES 199

APPENDIX I Perspective 205

APPENDIX II X-ray 208

APPENDIX III Preprint 217

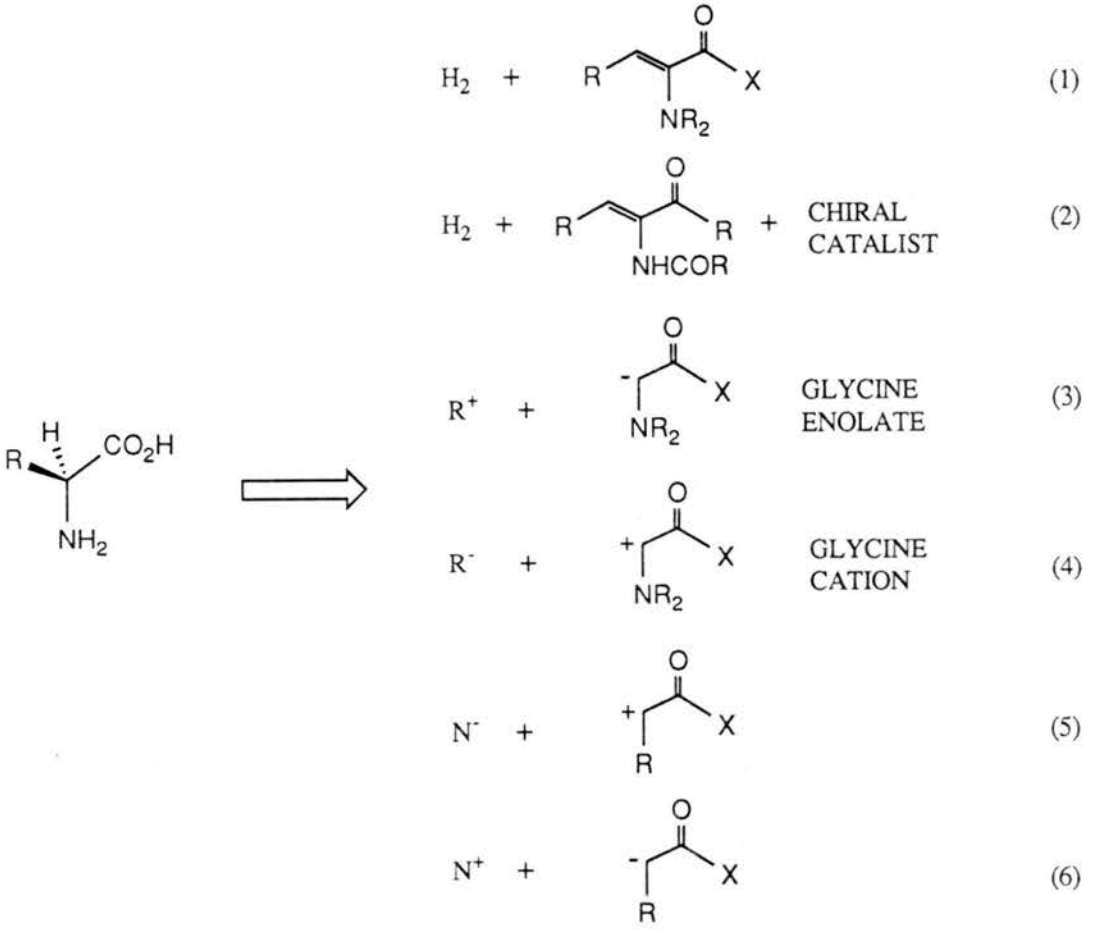
CHAPTER 1

INTRODUCTION

A. Background

α-Amino acids[1] play a pivotal role in biology and chemistry being the fundamental building blocks of proteins and peptides. They also serve as precursors of many kinds of secondary metabolites that have important biological roles.[2] In addition, a variety of α-amino acids have been used as optically active starting materials for the construction of a wide range of complicated structures.[3] The number of naturally occurring α-amino acids is currently approaching 1000.[4] Non-proteinogenic, unnatural α-amino acids have recently attracted organic chemists in connection with design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms. As a consequence, numerous and versatile approaches to the synthesis of proteinogenic, natural and unnatural amino acids in optically active form have been reported in the past decade.

The established methods for the asymmetric synthesis of amino acids can be divided into six categories. The highly stereoselective hydrogenation of chiral, nonracemic dehydro amino acid derivatives (Eq. 1)[5] or the asymmetric hydrogenation of prochiral dehydro amino acid derivatives (Eq. 2)[6] suffers from the range of substituents accepted in the β-position. Chiral glycine equivalents serve as useful α-amino acid templates undergoing



homologation *via* carbon-carbon bond formation at the α-position through nucleophilic carbanion alkylation (Eq. 3)[7] or electrophilic carbocation substitution (Eq. 4).[8] In addition both nucleophilic amination (Eq. 5)[9] and electrophilic amination (Eq. 6)[10] of optically active carbonyl derivatives have very recently been developed. The following paragraphs briefly outline the most outstanding and preparatively useful methods to synthesize a wide variety of optically active α-amino acids *via* carbon-carbon bond formation of chiral glycine enolate equivalents at α-position.

B. Synthesis of α-Amino Acids *via* Nucleophilic Glycine Equivalents

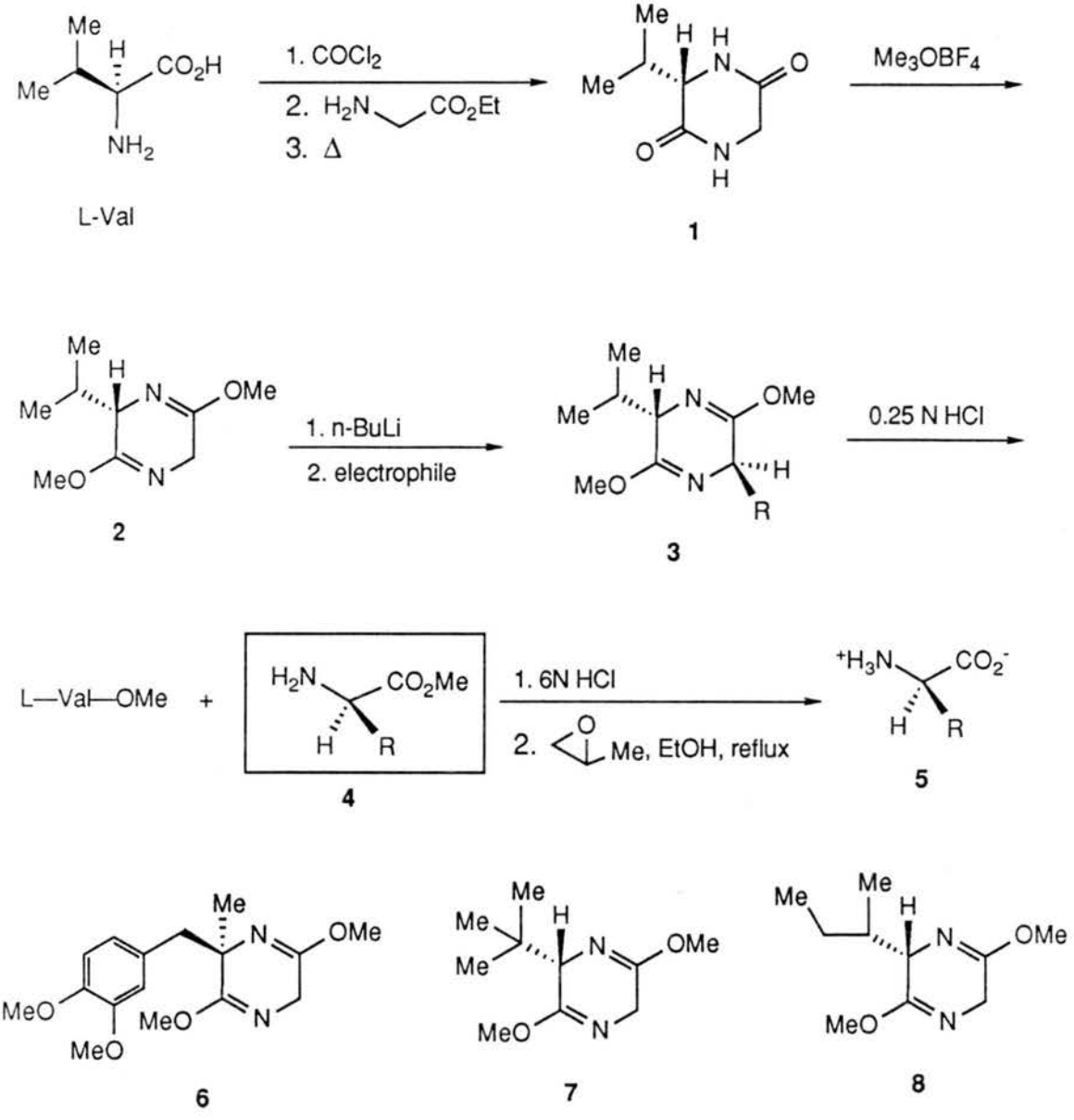
Chiral glycine enolates have been studied extensively for the asymmetric synthesis of amino acids. The syntheses employ either acyclic glycine imino esters (Schiff bases) containing a chiral auxiliary or chiral heterocycles possessing a glycine moiety within the ring. In addition, the glycine enolates of transition metal complexes have recently been investigated.

1. Bis-Lactim Ethers

Schöllkopf and coworkers have devised one of the most versatile and general methods to prepare a large variety of amino acids.[11] Their protocol utilizes the bis lactim ether **2** derived from the cyclic dipeptide **1** which is obtained by coupling L-valine with glycine. The metallation with n-butyllithium at low temperature and subsequent alkylation occurs smoothly to afford the *anti*-homologated heterocycle **3** in good yields and with high diastereoselectivity (60->95%). Hydrolytic cleavage of the heterocycle **3** with dilute HCl at ambient temperature furnishes the new amino methyl ester **4** and L-valine methyl ester which can be recovered and recycled. More vigorous condition (6N HCl, reflux) gives the free amino acid zwitterion **5**(Scheme 1).[12]

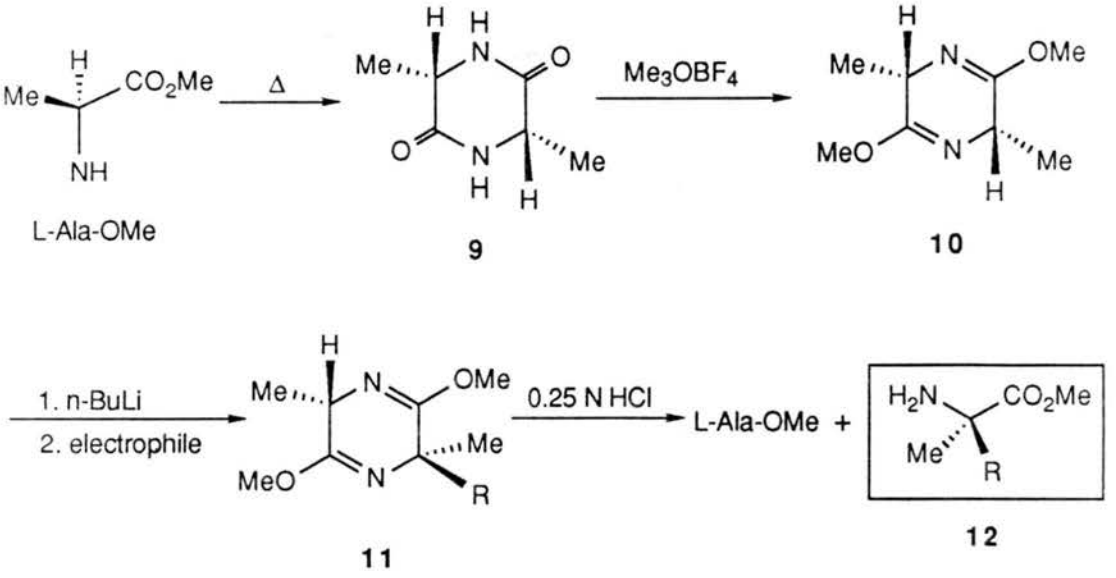
Several other bis-lactim ethers have been prepared following the standard protocol. The templates derived from (S)-O,O-dimethyl-α-methyldopa and glycine (**6**).[13] L-terleucine and glycine (**7**),[14] and L-isoleucine and glycine (**8**)[15] have all been reported as useful templates for synthesizing optically active amino acids. The Val-Gly system is commercially available in both enantiomeric forms.

SCHEME 1



Schöllkopf has also synthesized the symmetrical bis-lactim **10** by self-condensation of L-alanine methyl ester and subsequent O-methylation to synthesize the α,α-disubstituted amino acid methyl ester **12** (Scheme 2).[16] The alkylation of the heterocycle **10** takes place to afford **11** in very good yield. The electrophile is introduced *anti-* to the methyl group with high

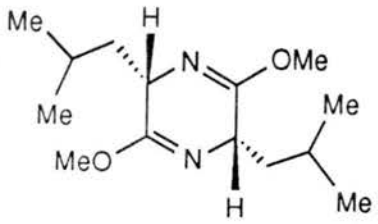
SCHEME 2



stereoselectivity (91->95%). The homologated bis-lactim ether **11** is converted into the α-methyl-α-alkyl amino acid methyl ester **12** in good yield.

Another symmetrical Leu-Leu bis-lactim ether **13**[17] has been prepared by cyclo-dimerization of L-leucine and sequential O-methylation following the same protocol as the dimethyl bis-lactim **10**. Electrophiles are added *anti-* to the leucine moiety with high diastereoselectivity (85->95%). With these very hindered lactim ether adducts, however, hydrolysis to the amino acid methyl esters proceeds slowly and was noted to even fail in some cases.

The Val-Ala bis-lactim ether **14**[18] is one of the most useful reagents available for preparing a wide array of α-methylated amino acids that are of considerable current biomedical interest. The reagent is prepared in the usual way from optically active L- or D-valine and D,L-alanine ethyl ester. The bis-lactim ether then, is a 1:1 diastereomeric mixture; this is of no consequence since, the metallation step converts this d,l-center to a planar carbanion. It is quite interesting that the metallation is highly *regioselective* resulting in exclusive deprotonation at the alanine stereogenic center. Since the



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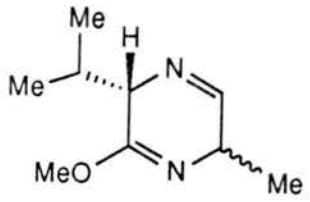


14

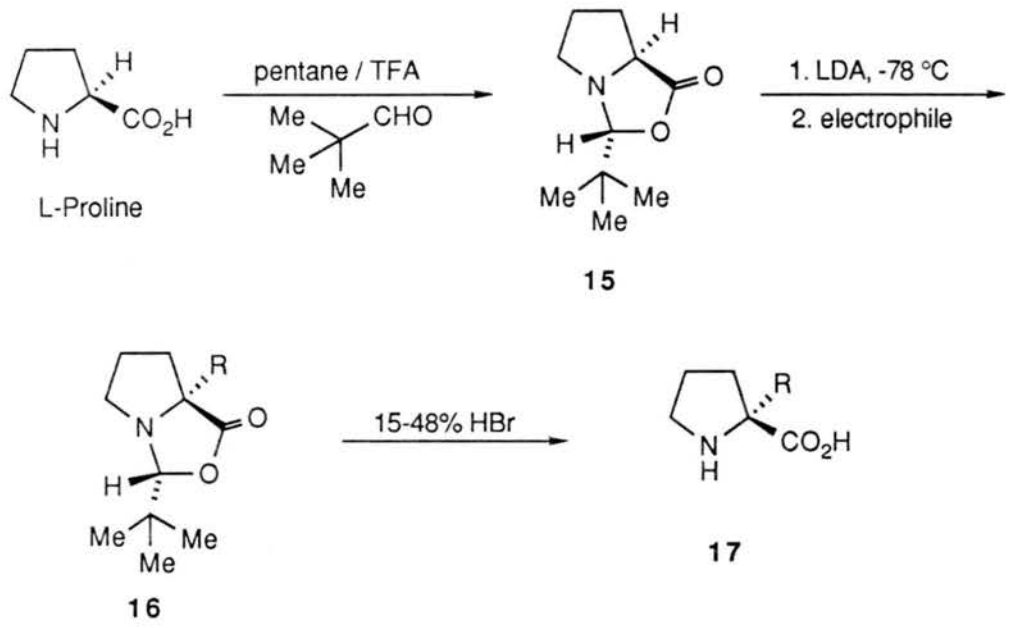
carbanion formation is done under kinetic control, this result is undoubtedly attributable to the relative steric accessibility of the Ala methine over the Val methine. The heterocycle **14** was observed to give exceptionally high diastereomeric excess (typically >95%) in alkylations of the lithiated derivative.

The bis-lactim ether method provides a powerful and versatile tool for preparing a large array of α-amino acids and α,α-disubstituted amino acids in optically active form. The major weaknesses of the bis-lactim ether method involve some of the difficulties associated with the hydrolysis of the derivatized bis-lactim ethers to the amino acid methyl esters and finally (under harsher conditions) to the free amino acids. The separation of chiral auxiliary from the new amino acid can also be problematic especially in instances where the boiling points of the two products are similar.

2. Imidazolidinones, Oxazolidinones and Oxazolines

Seebach and associates have made an extensive contribution to the practical asymmetric synthesis of amino acids *via* the formation of various cyclic aminals of numerous amino acids and the subsequent enolate alkylation of such systems with a high degree of diastereoselectivity. The first system reported on was the enolate alkylation of the bicyclic aminal[15] prepared from L-proline and pivaldehyde (Scheme 3).[19] Treatment of L-proline with pivaldehyde in the presence of TFA gives rise to a single diastereomer in high yield with the relative configuration shown. The enolate generation of **15** with LDA at low temperature and subsequent quenching

SCHEME 3



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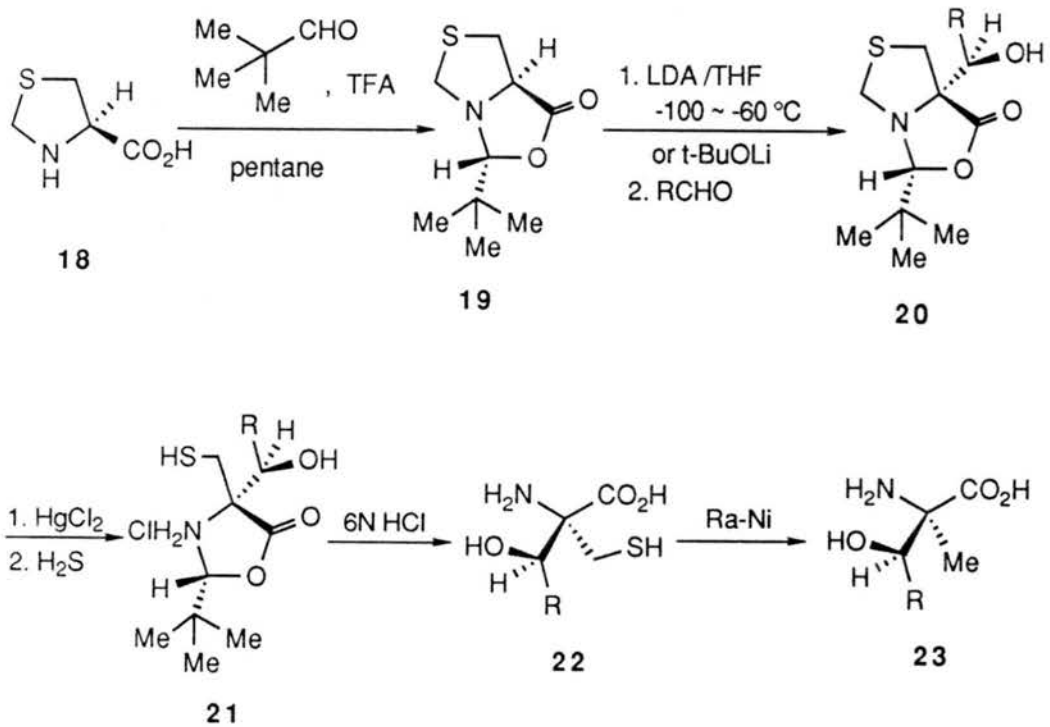
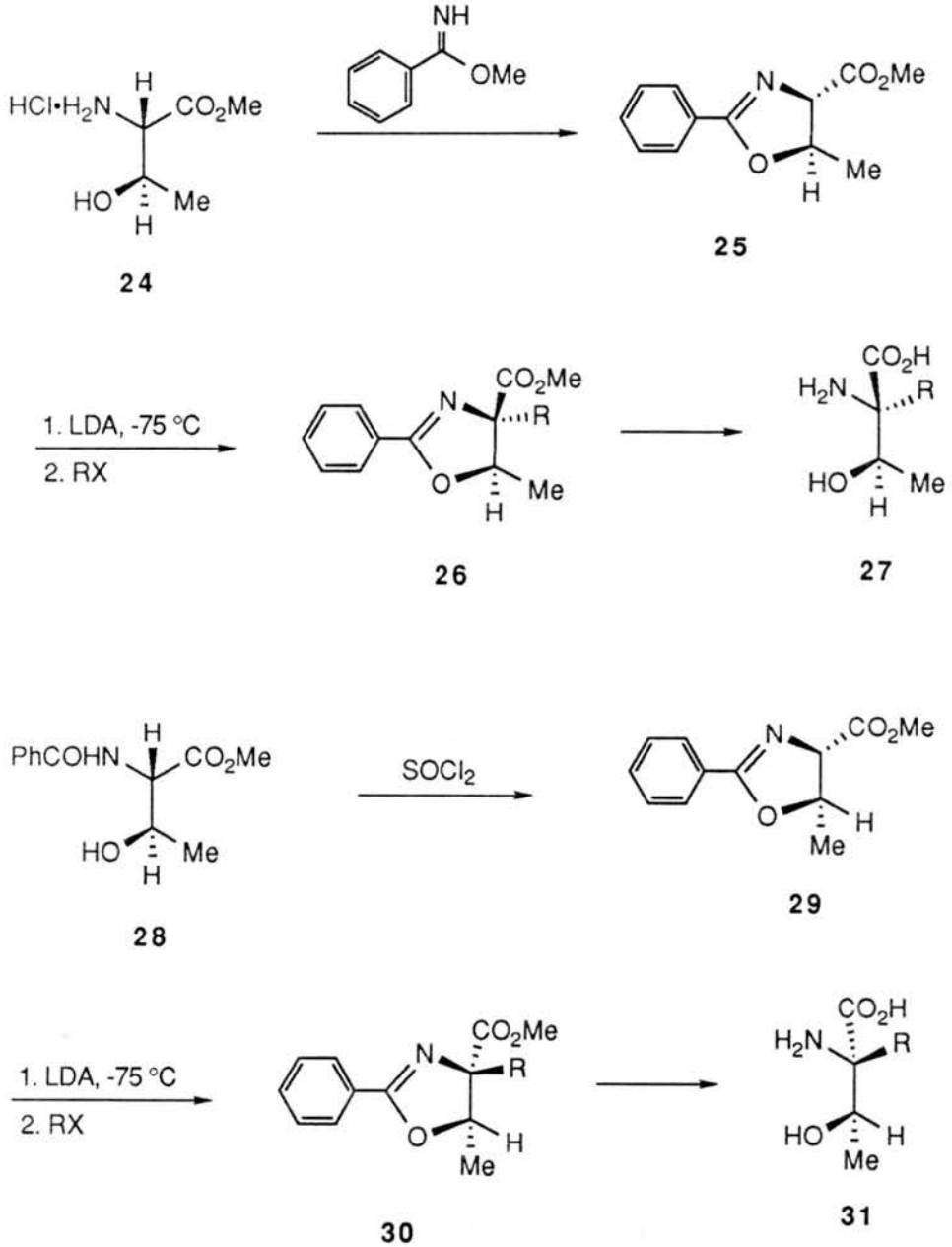


SCHEME 5



with an electrophile affords **16** in good to excellent yields with an excellent degree of stereoselectivity (>99%). The alkylation proceeds with *retention* of configuration. The hydrolysis of the homologated oxazolidinone to the free amino acid **17** requires harsher conditions (15-48% HBr at ambient to reflux temperatures), and gives low yield or fails in the some case of the bulkier α-R residue.

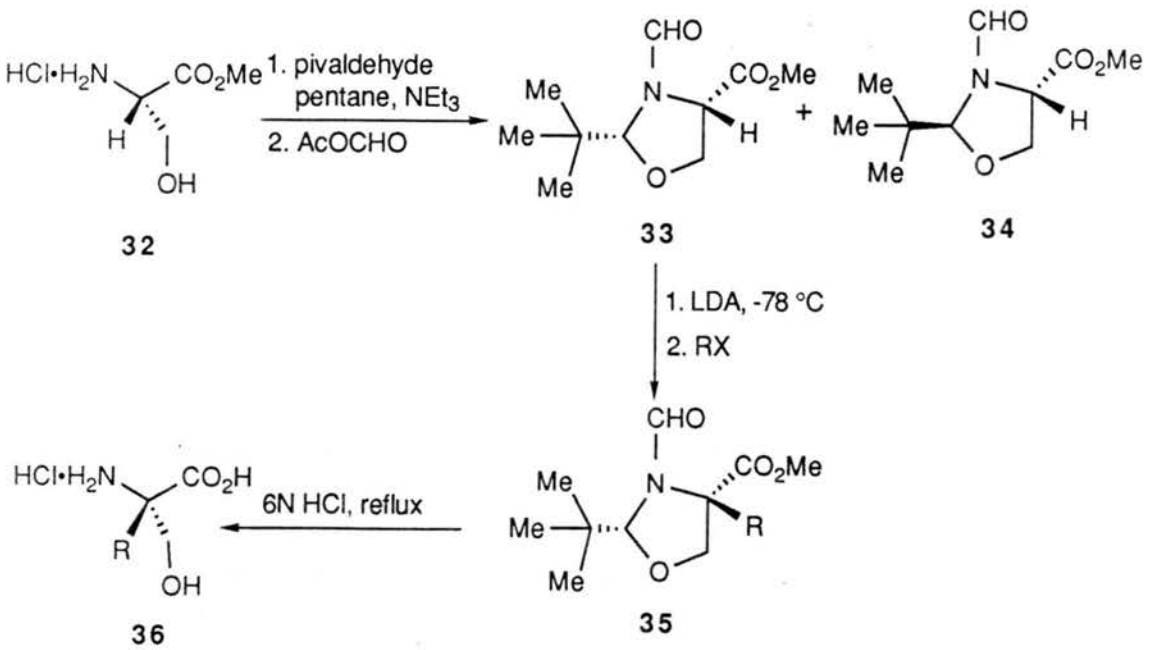
Another bicyclic aminal **19** was prepared from the cyclic hemithio aminal **18** derived from L-cysteine (Scheme 4).[20] Enolization with LDA or lithium t-butoxide followed by aldol condensation provided the carbinols **20**. The diastereoselectivity of C-C bond formation at the α-center of the amino acid moiety is >99% de; the diastereoselectivity at the carbinol center is very good ranging from 65-96% ds.

Seebach prepared a threonine-derived template for homologation of the α-carbon (Scheme 5).[21] Condensation of threonine methyl ester with methyl imino benzoate furnished the *trans*-isomer **25**; the corresponding *cis*-isomer **29** is obtained from N-benzoyl threonine methyl ester and thionyl chloride. Enolate formation with LDA in THF at -75°C followed by addition of various electrophiles affords the adducts **26** and **30** with high diastereoselectivity (60->98%) respectively. The electrophile approaches the enolate from the face *anti*- to the threonine methyl residue. The free amino acids **27** and **31** are obtained in high yield by hydrolysis of the oxazolines with refluxing 6N HCl and ion exchange dehydrochlorination.

The serine templates **33** and **34** were prepared by acetalization with pivaldehyde and N-formylation (Scheme 6)[22]; the major diastereomer **33** is separated from the minor component by crystallization. Enolate formation and homologation with several electrophiles show excellent diastereoselectivity (>95%); the electrophiles attack *anti*- to the t-butyl residue. The homologated oxazolidine **35** is converted into the α-functionalized serine derivatives **36** by refluxing 6N HCl.

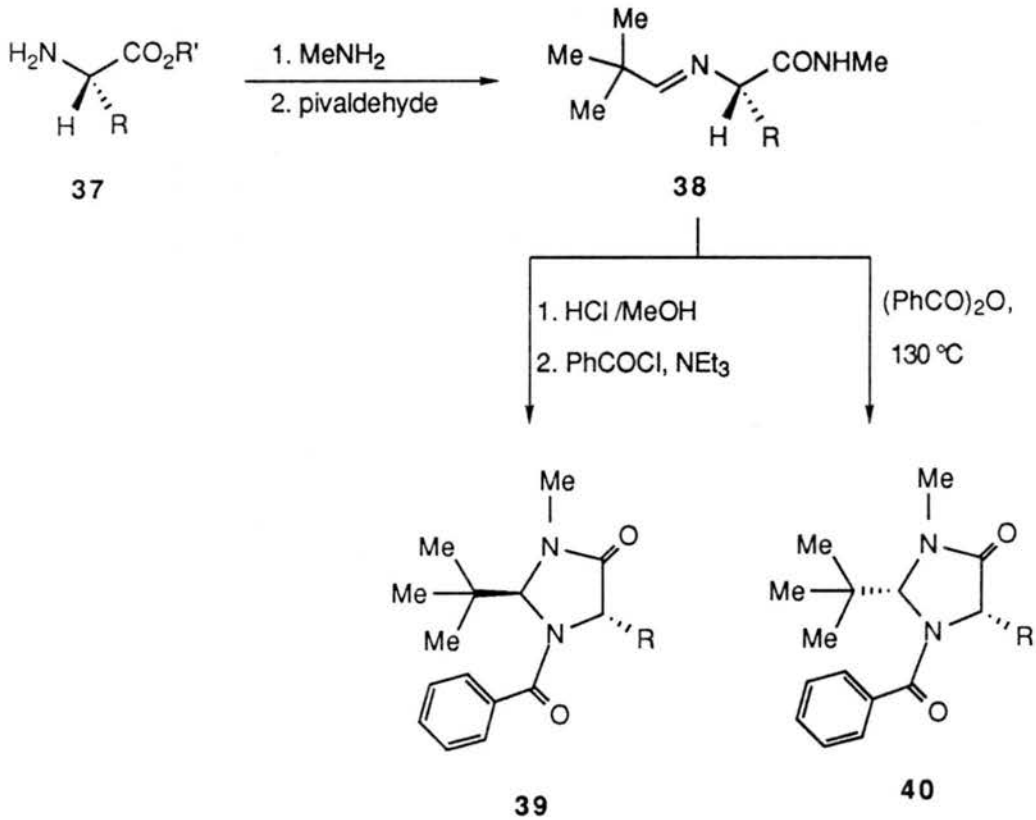
The above investigations cultimated in the development of a general and practical approach to preparing a wide variety of novel amino acids employing optically active oxazolidinone and imidazolidinone derivatives of several amino acids. The general method for the imidazolidinones is

SCHEME 6



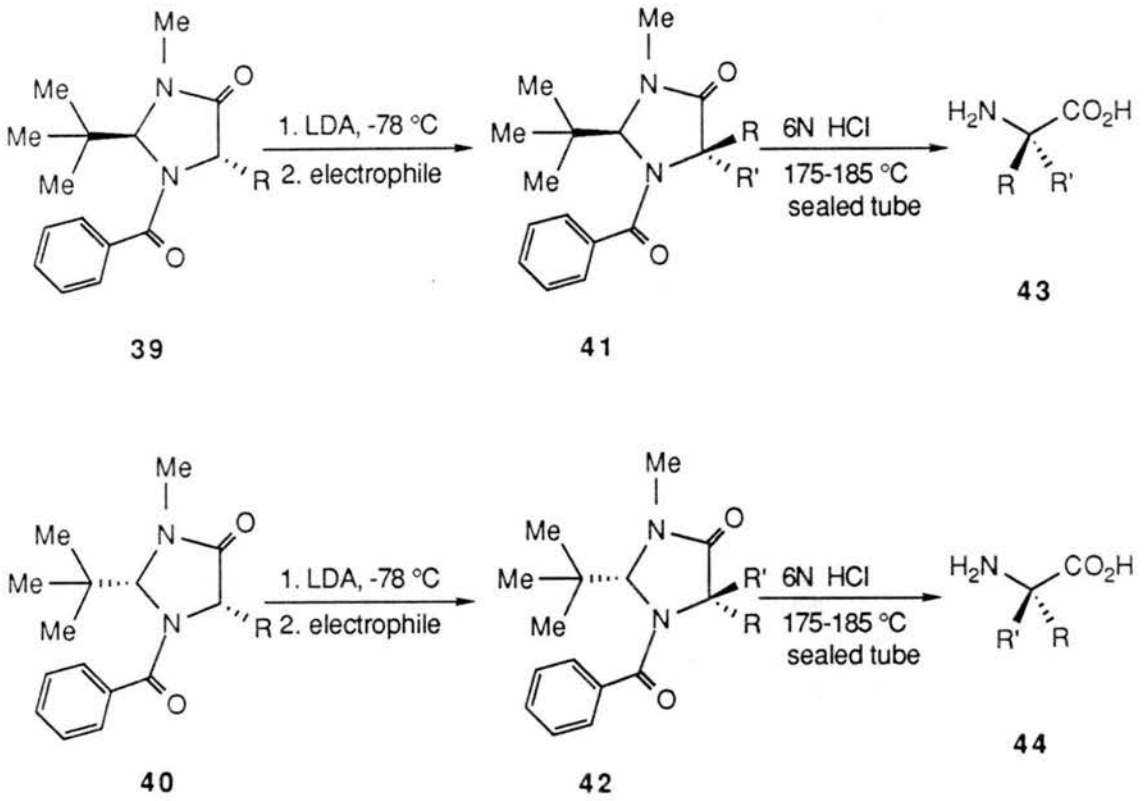
32 33 34 35 36

SCHEME 7



37 38 39 40

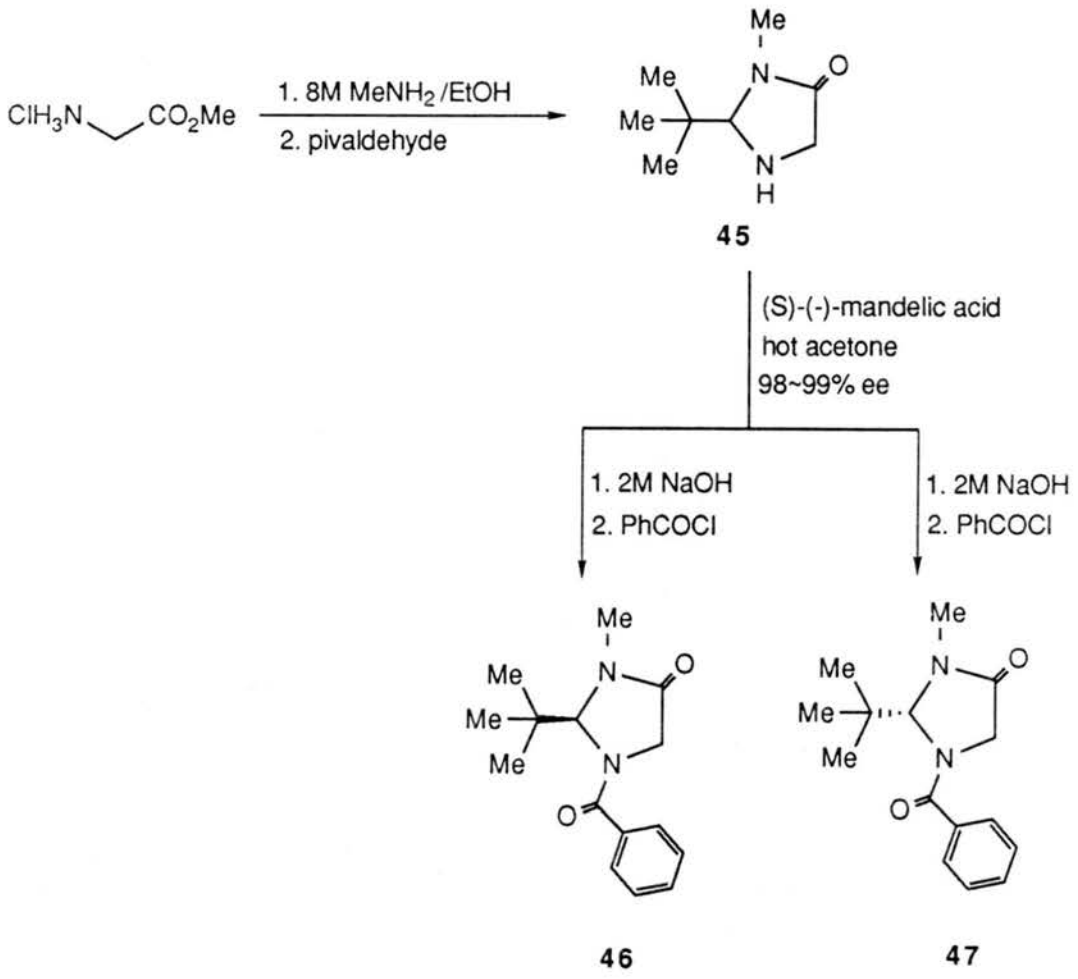
SCHEME 8



illustrated in Scheme 7.[23] Amino acid methyl or ethyl esters **37** are treated with concentrated methyl amine to form the corresponding methyl amides. Imine formation with pivaldehyde provides the pivaloyl imines **38**. Treatment with methanolic HCl followed by acylation with benzoyl chloride effects stereoselective ring closure to the *anti*-imidazolidinones **39** as the major product. The corresponding *syn*-isomers **40** are obtained by treatment of **38** with benzoic anhydride at 130°C. Enolate homologation of these derivatives (Scheme 8)[24] proceeds in generally good yields and excellent diastereoselectivities (>90%). The final hydrolysis, under rather severe conditions (typically 6N HCl at 175-185°C in a sealed tube) affords the free amino acids.

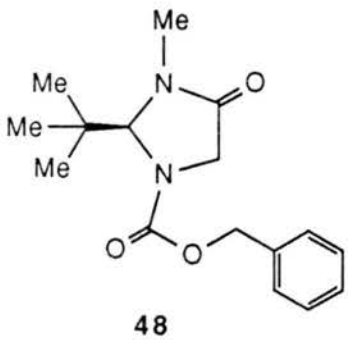
The optically active glycine-derived templates **46** and **47** were prepared by resolution of the racemic substance **45** *via* the derived mandelate

SCHEME 9

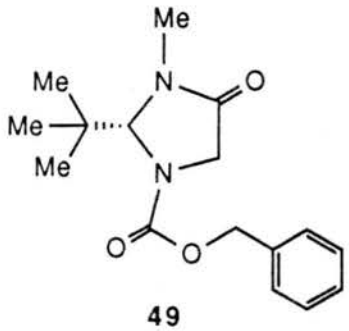


salts (Scheme 9).[25] The corresponding N-CBz and N-t-Boc templates (**48-51**) in each enantiomorphic form are now commercially available.

Enolate functionalization of the benzoylated glycine amide **46** with alkyl halides proceeds with a high degree of stereoselectivity (>95%). Alkylation occurs in *anti-* direction to the t-butyl group (Scheme 10).[26] The condensation with aldehydes revealed that the benzoyl group migrates to the incipient alkoxides. These reactions proceed with high *threo*-selectivity furnishing the β-hydroxy-α-amino acids **54** after hydrolysis in boiling 6N HCl (Scheme 11).[27]



48



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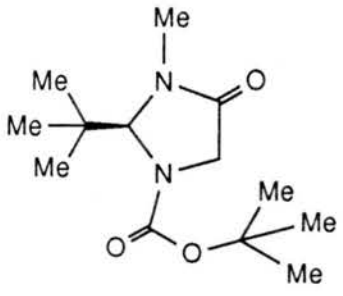

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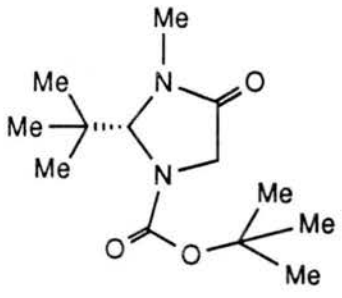
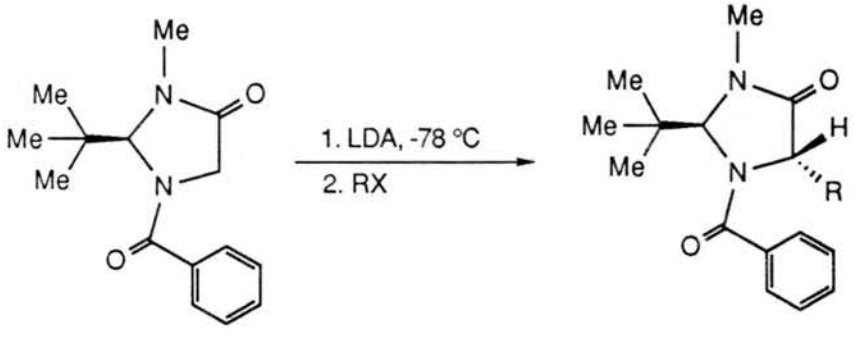


51

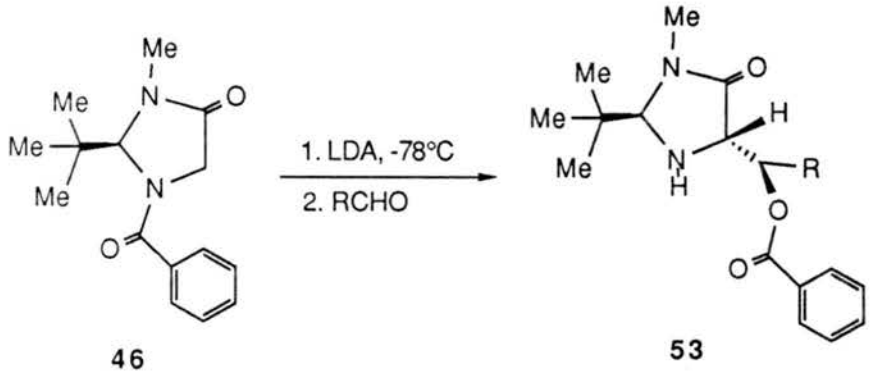
SCHEME 10



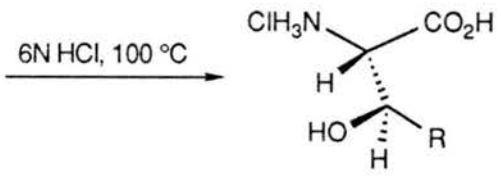
46 52

The optically active oxazolidinones derived from alanine, phenylalanine, valine and methionine (Scheme 12)[27] were prepared. The general protocol involves reaction of the sodium salt of the free amino acid with pivaldehyde to furnish the corresponding imine. The imine is then cyclized in the presence of benzoyl chloride to give a *syn/anti* mixture of the desired oxazolidinones **56**. In all cases the *syn*-isomer is the major product that must be separated from the minor *anti*-isomer. Enolization with LDEA and

SCHEME 11

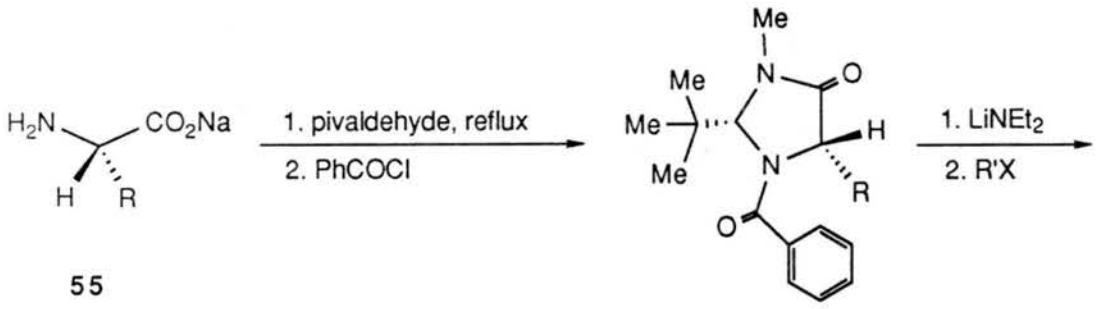


46 53

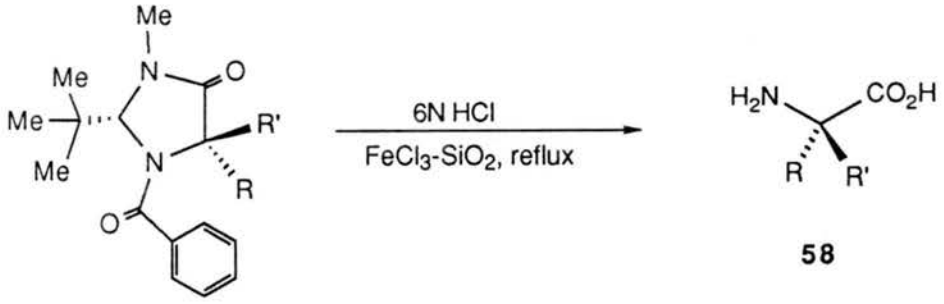


54

SCHEME 12

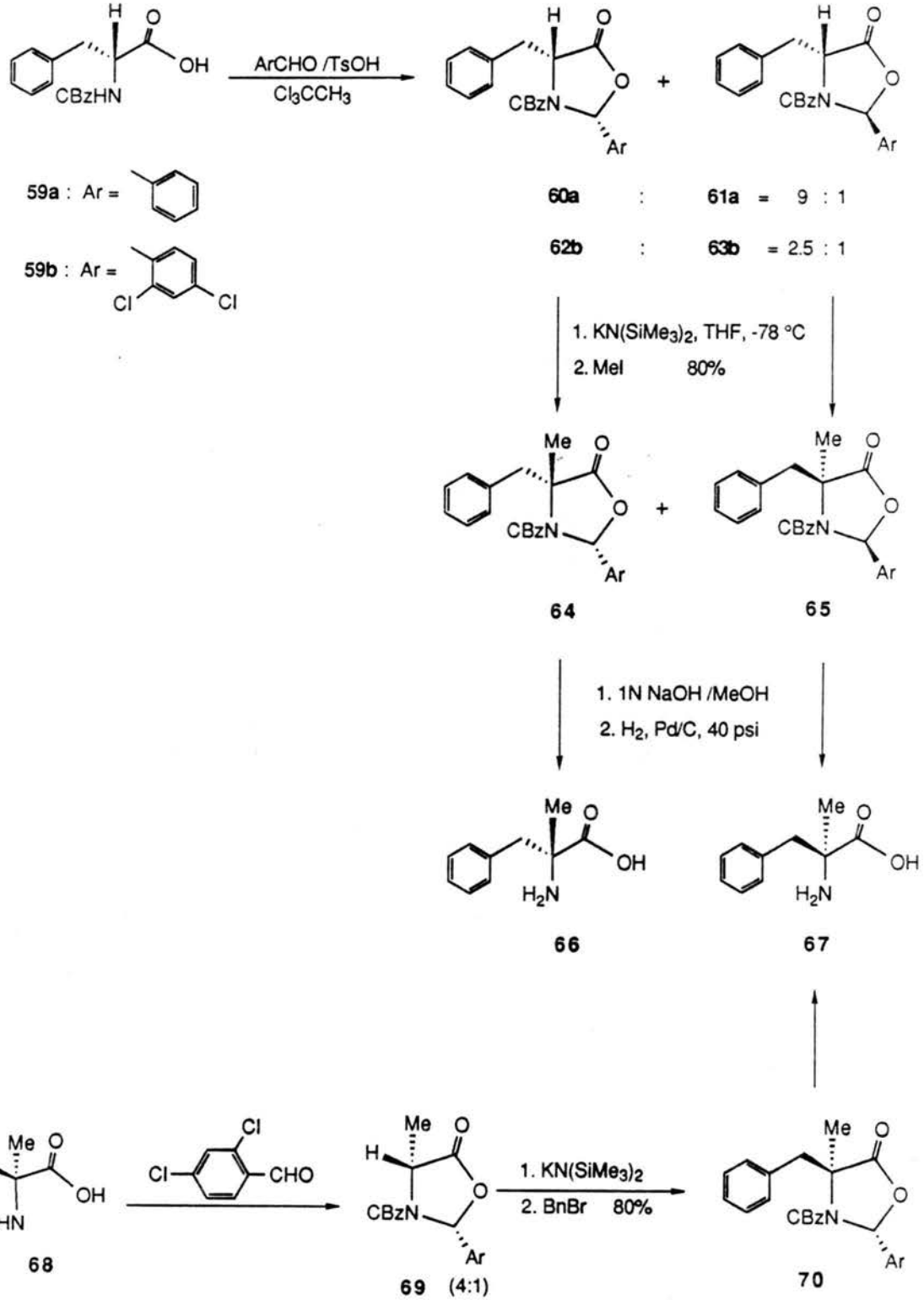


55 56



57 58

SCHEME 13


ArCHO /TsOH
Cl3CCH3
59a : Ar =
59b : Ar =
60a : 61a = 9 : 1
62b : 63b = 2.5 : 1
1. KN(SiMe3)2, THF, -78 °C
2. MeI 80%
64
65
1. 1N NaOH /MeOH
2. H2, Pd/C, 40 psi
66
67
68
69 (4:1)
1. KN(SiMe3)2
2. BnBr 80%
70

subsequent treatment with alkyl halides provide **57** in good yields and high diastereoselectivity (>85%). The α-functionalized substances are hydrolyzed by refluxing 6N HCl in the presence of $FeCl_3$-SiO_2 to give the α-disubstituted amino acids **58**.

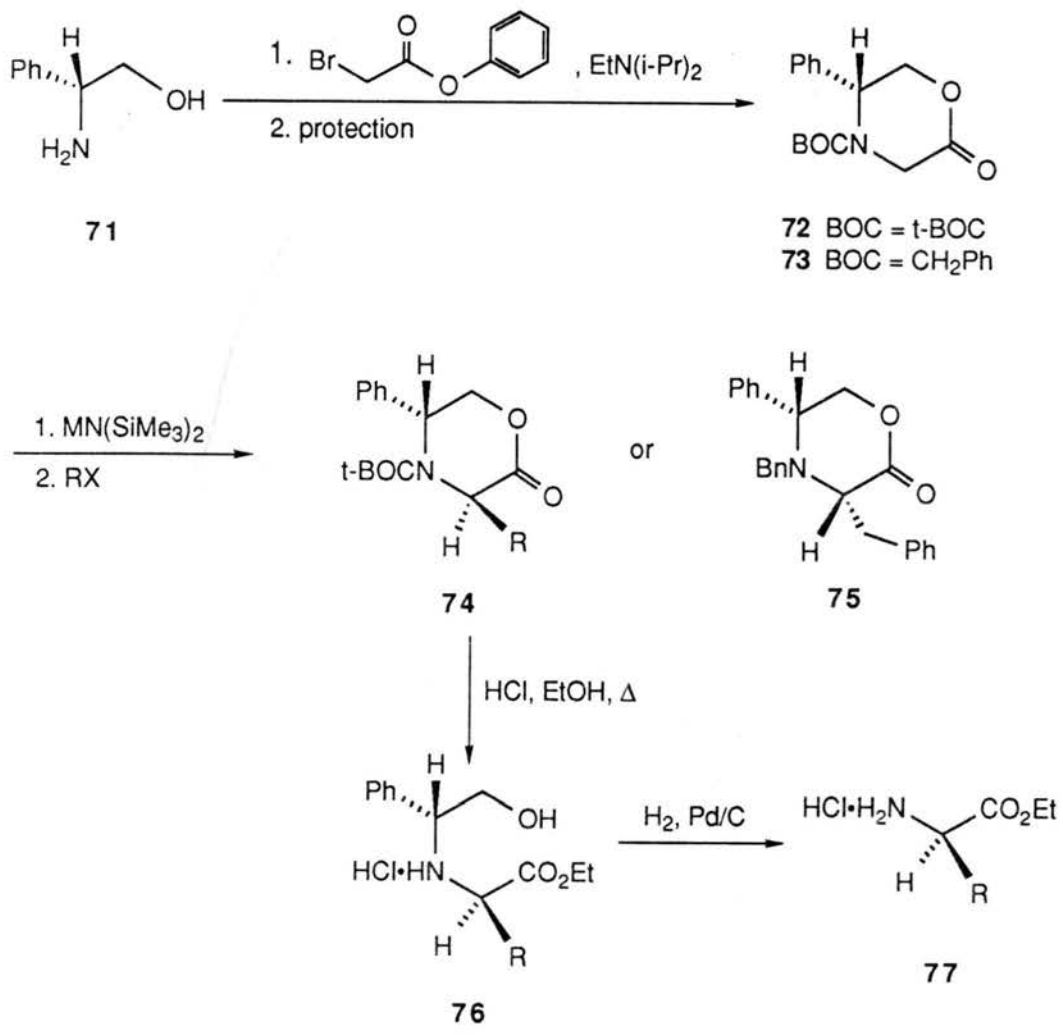
Karady and coworkers[28] reported on oxazolidinones derived from benzaldehyde or 2,4-dichlorobenzaldehyde and phenylalanine or alanine as shown in Scheme 13. In all cases, the *syn*-isomers (**60a/69**) were formed as the major products. Enolate formation with potassium bis(trimethylsilyl)amide and alkylation with either methyl iodide or benzyl bromide provided the adducts **64**, **65** and **70**, respectively. In all cases the electrophile approaches from the face *anti*- to the aromatic acetal moiety. The α-methyl phenylalanine derivatives **66/67** are produced by treatment with methanolic sodium hydroxide and catalytic hydrogenation.

The extensive use of stereoselective enolate functionalizations of the Seebach heterocycles provides a useful and practical approach to the asymmetric synthesis of non-proteinogenic amino acids. An inherent limitation is the somewhat harsh acidic conditions required for the final deblocking to the final amino acids. For α-R groups that are inherently acid stable, this method should become particularly useful for preparing α,α-disubstituted amino acids.

3. Oxazinone

Dellaria and Santarsieo[29] have prepared the 5-phenyl-2,3,5,6-tetrahydro-4H-oxazin-2-ones **72** and **73** from phenylglycinol as shown in Scheme 14. Enolization and treatment with alkyl halides gave good to excellent yields of *anti*- alkylation adducts **74** with high diastereoselectivities (78->99%). Curiously, the N-benzyl substrate affords the *syn*-product **75** as the major component (*syn:anti* = 17:1). Conversion of **74** to the corresponding

SCHEME 14



amino acid ethyl esters is accomplished by acidic hydrolysis of the lactone to the ethyl ester HCl **76** and subsequent catalytic hydrogenation to the ethyl ester HCl **77**.

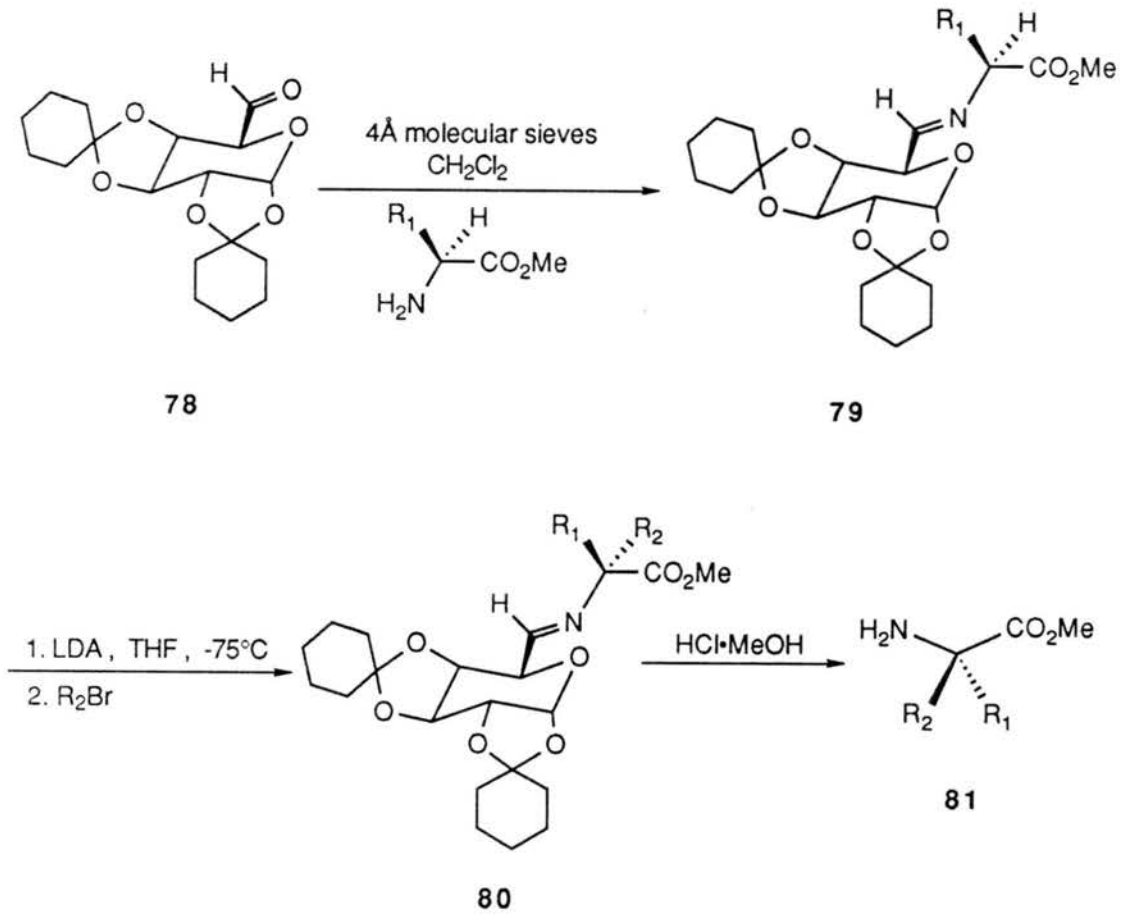
4. Schiff Bases

Numerous groups have investigated the enolate alkylation of Schiff bases derived from glycine and other amino acids to access optically active amino acids and α-substituted amino acids. The major conceptual advantage of this general approach is the intrinsic ability to recover and reuse the chiral

auxiliary as well as the inherent versatility of having access to a wide range of amino acids from a single template.

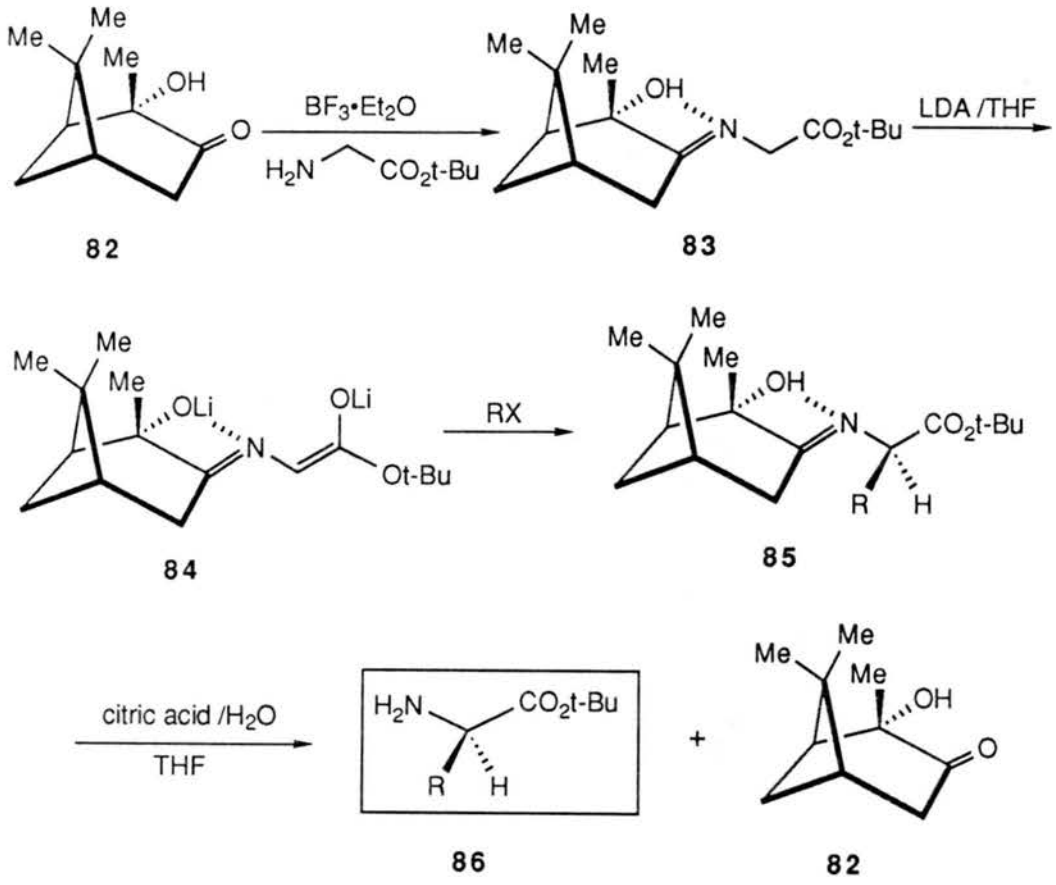
Schöllkopf[30] has recently devised the enolate alkylation of galactodialdehyde aldimines derived from valine, leucine and isoleucine. As shown in Scheme 15, condensation of Val, Leu, or Ile with **78** in the presence of molecular sieves furnishes the aldimines **79**. Enolate formation with LDA in THF followed by alkylation provides the homologated derivatives **80**; subsequent hydrolysis with methanolic HCl provides the amino acid methyl esters **81**. The diastereoselectivities of the alkylations are generally good to excellent with a broad range of 23->95%.

SCHEME 15



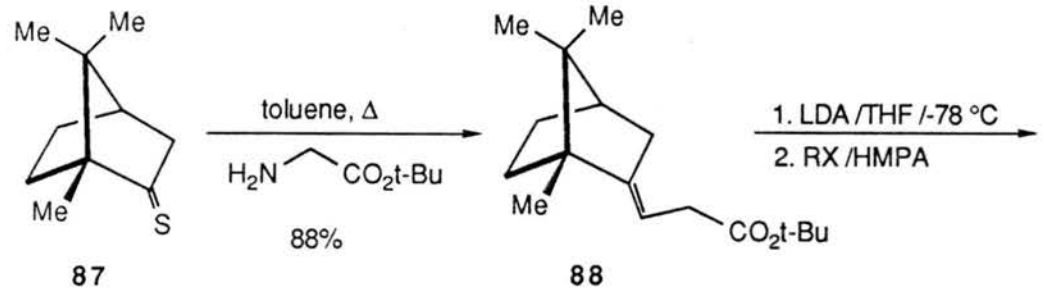
78 **79** **80** **81**

SCHEME 16

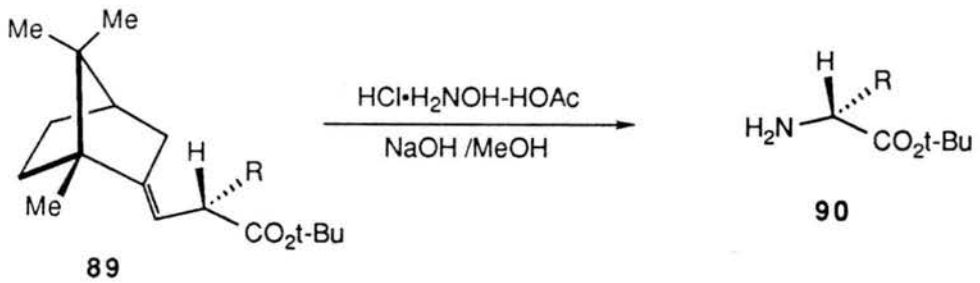


82 83 84 85 86 82

SCHEME 17



87 88



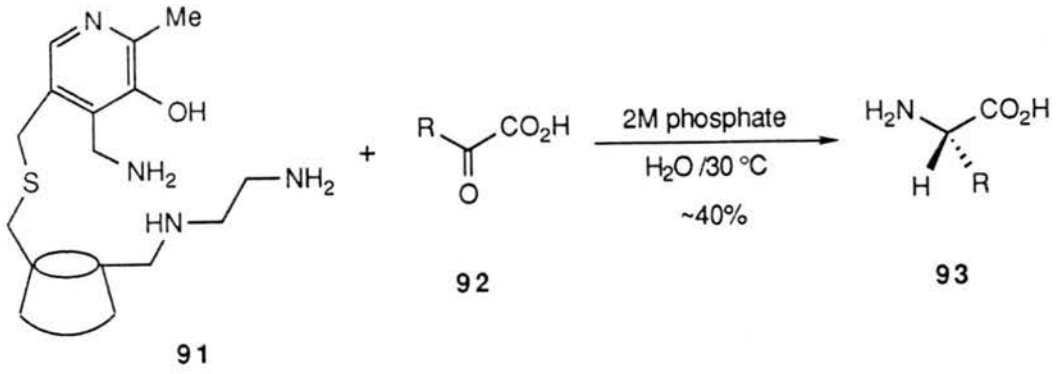
89 90

One of the first reports[31] on the stereoselective alkylation of glycine imines was that by Yamada and associates in 1976. As shown in Scheme 16, condensation of (1S,2S,5S)-2-hydroxypinan-3-one **82** with glycine t-butyl ester in the presence of $BF_3 \cdot Et_2O$ furnishes the ketimine **83**. Treatment with 2 equiv. LDA in THF gives the dilithio species that the authors formulate as the internally chelated species **84**; subsequent alkylation proceeds stereoselectively to furnish **85** (66-83% de). Hydrolysis of the ketimine with aqueous citric acid in THF provides the t-butyl esters **86**. The authors note that the ketol **82** can be recovered and is available in both enantiomeric forms *via* the precursors (+)- and (-)-α-pinene.

McIntosh and coworkers[32] reported on the utility of camphor-derived imines of glycine in enolate alkylations. Conversion of camphor to the reactive thione **87** and subsequent imine formation proceeds in good yield to furnish the key derivative **88**. Enolate formation with LDA and alkylation in the presence of HMPA provides the homologated imines **89**. The wide range of stereoselectivities was observed (0-96% de). Hydrolysis of the imine by exchange with hydroxyl amine furnishes the t-butyl esters **90**. Steric hindrance of the camphor imine makes the cleavage somewhat problematic and only one example (t-butyl phenylalaninate) is reported. The resulting camphor oxime is separated from the amino acid ester by a simple extraction procedure.

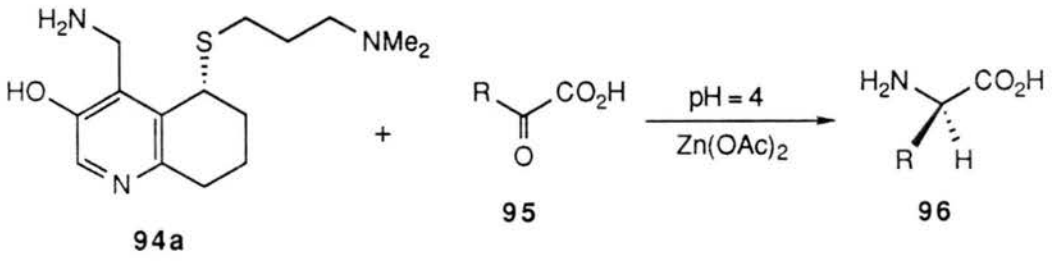
Breslow and coworkers[33] reported on the use of modified pyridoxamine mimics for stereospecific transaminations. In one approach, pyridoxamine was attached to a modified β-cyclodextrin containing both a binding domain and an attached basic group to effect stereospecific tautomerization (Scheme 18). It was found that aromatic ketoacids would bind effectively inside the cavity and resulted in highly stereoselective transaminations to the L-amino

SCHEME 18

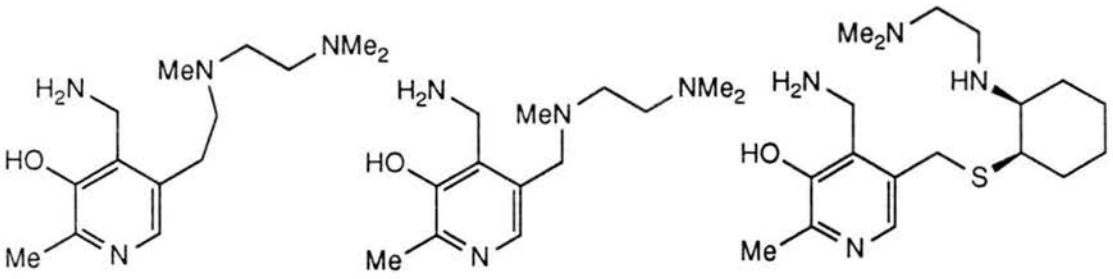


91 92 93

SCHEME 19

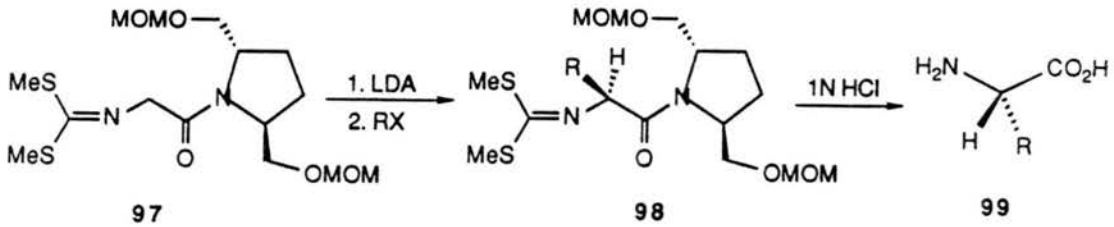


94a 95 96



94b 94c 94d

SCHEME 20



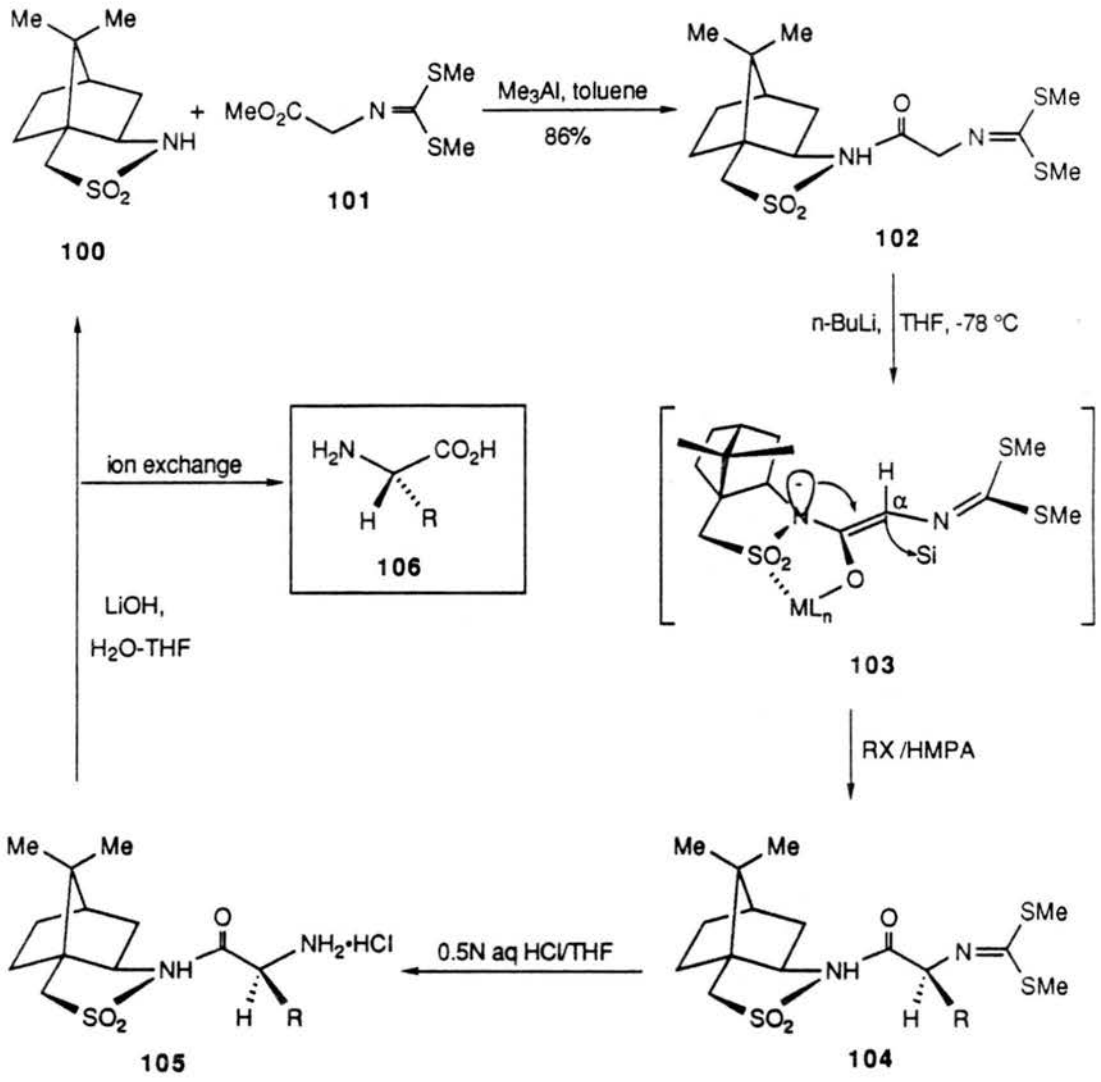
97 98 99

acids **93** (>90% ee) although in modest chemical yields. Simple aliphatic keto acids gave poor stereoselectivities. It is quite significant, however, that the racemization-prone phenylglycine could be obtained in 96% ee which is a powerful testament to the mildness of the reaction conditions. In another study (Scheme 19), the bicyclic system **94a** was shown to lead to stereoselective transaminations with a wider substrate specificity than the cyclodextrin model; D-alanine, D-norvaline, and D-tryptophan being obtained in 86-92% ee and 68-89% yields. Modifications of this system led to the pyridoxamines **94b-d** which similarly incorporate the critical diamine side-chain substituent. It was found that **94c** and **94d** give the best rate accelerations while **94b** seems to have too short a tether to facilitate the crucial proton transfer. The major limitation to the practical use of **94a** is the long multi-step (ca. 18 steps) syntheses and attendant resolution required for its preparation; the newer systems **94c,d** being somewhat simpler to prepare.

Katsuki and coworkers[34] have recently devised a potentially quite useful glycine enolate equivalent as shown in Scheme 20. Glycine amide **97** was found to undergo smooth and highly stereoselective enolate alkylation with active electrophiles affording the adducts **98**. Simple acid hydrolysis and ion-exchange chromatography furnished the free amino acid **99** in excellent chemical yields and high % ee's (>95%).

Oppolzer[35] has recently prepared a related imine derived from a camphor-sultam as an amino acid template (Scheme 21). Acylation of the sultam **100** with methyl N-[bis(methylthio)methylene]glycinate (**101**) in the presence of trimethylaluminum furnishes, after crystallization, the glycinate **102**. Successive treatment of **102** with n-BuLi in THF (-78°C) and alkyl halides in HMPA (-55°C → r.t.) provides the homologated imine **104** in a high degree of diastereoselectivity (94.7-98.4% de). The chelated (Z)-enolates

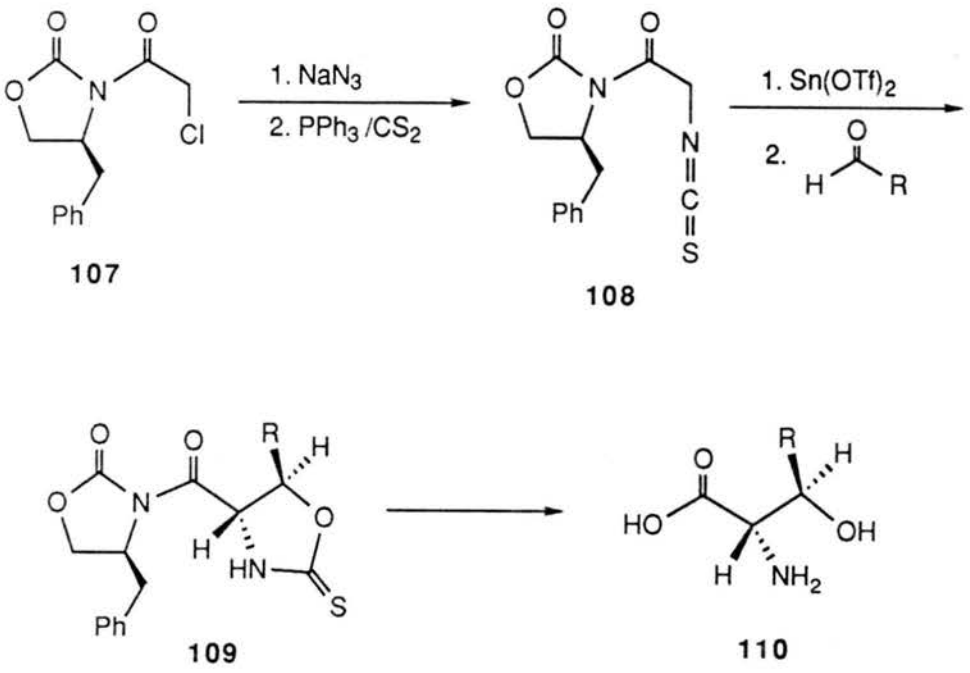
SCHEME 21



103, which are formed under kinetic control, undergo alkylation from the C(α)-*si*-face, opposite to the lone electron pair on the sultam-nitrogen atom. Selective N-deprotection of **104** by mild acidic hydrolysis furnishes the amine hydrochlorides **105** which are directly saponified with LiOH to afford the amino acid **106** after simple extraction and ion exchange.

An ingenious and practical glycine enolate equivalent has been developed by Evans and Weber[36] as a means of constructing β-hydroxy-α-amino acids *via* aldol bond constructions. As shown in Scheme 22, the

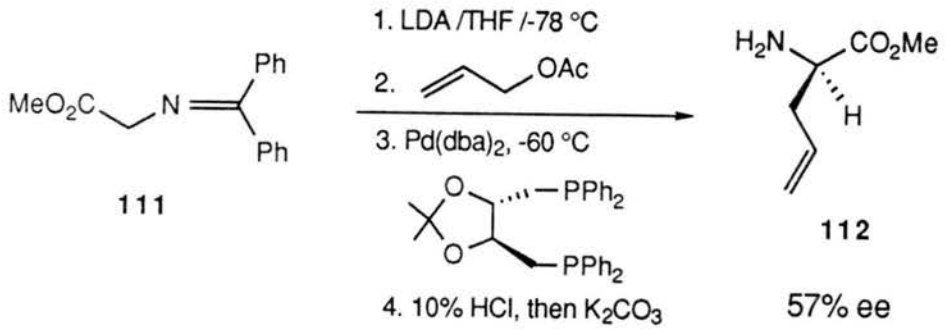
SCHEME 22



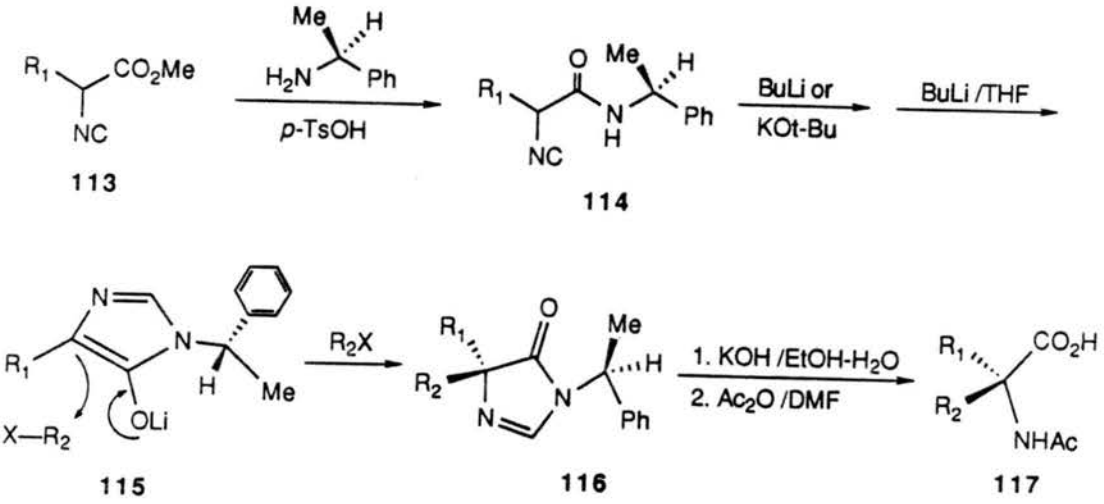
optically active chloroacetate derivative **107** is converted into the key, crystalline isothiocyanate **108** by reaction with sodium azide followed by reduction and thiocyanate formation. The stannous triflate mediated aldolization with aldehydes furnishes the *syn*-aldol adducts in both good yields and high levels of stereoselectivity (≥91:≤9). The initially formed aldol adducts undergo spontaneous cyclization on the isothiocyanate to form the thiono urethanes **109**. Final hydrolysis gave the free amino acid **110** in good yields.

Genet and associates[37] have initiated developing the asymmetric enolate alkylation of an achiral glycine Schiff base with optically active pi-allyl-palladium complexes. As illustrated in Scheme 23, the benzophenone imine of glycine methyl ester (**111**) is treated with LDA followed by allylation with allyl acetate and a palladium catalyst carrying an optically active phosphine ligand. After hydrolysis of the initial allylation adduct, allylglycine methyl ester (**112**) was obtained in 60% yield and 57% ee.

SCHEME 23



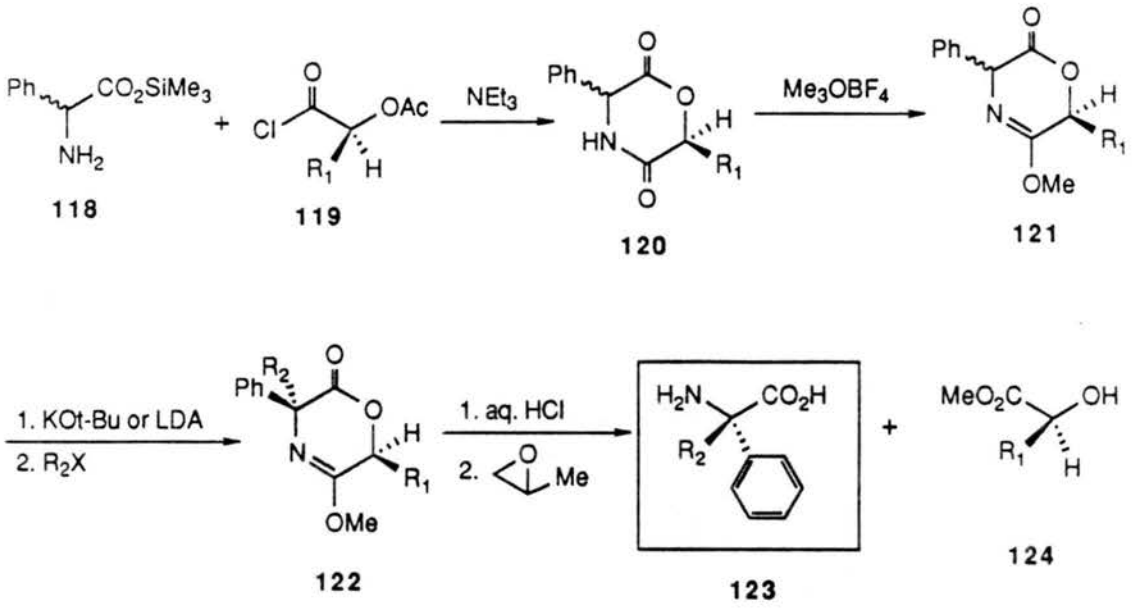
SCHEME 24



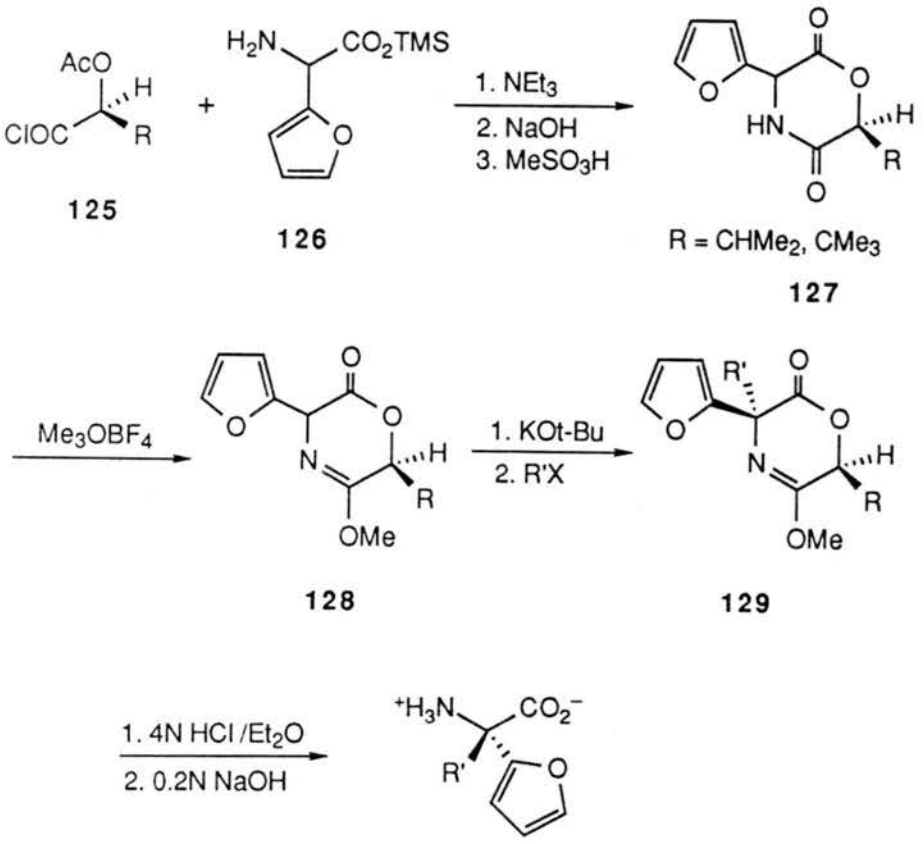
Schöllkopf and coworkers[38] found that optically active imidazolidinones could be prepared from alanine or phenylalanine isonitriles (**113**) and (S)-1-phenylethylamine (Scheme 24). The amide **114** is cyclized and immediately metallated to furnish the lithio-derivative **115** that undergoes stereoselective alkylation to provide the α,α-disubstituted derivative **116**. The % de in the alkylations was generally quite high (17-100%). Hydrolysis of the imidazolidinone to the corresponding amino acid is accomplished with ethanolic KOH followed by N-acetylation to the isolated products **117**.

In a related approach, Schöllkopf[39] reported the preparation of optically active 3,6- dihydro- 2H-1,4-oxazine-2-ones from a variety of optically active α-

SCHEME 25



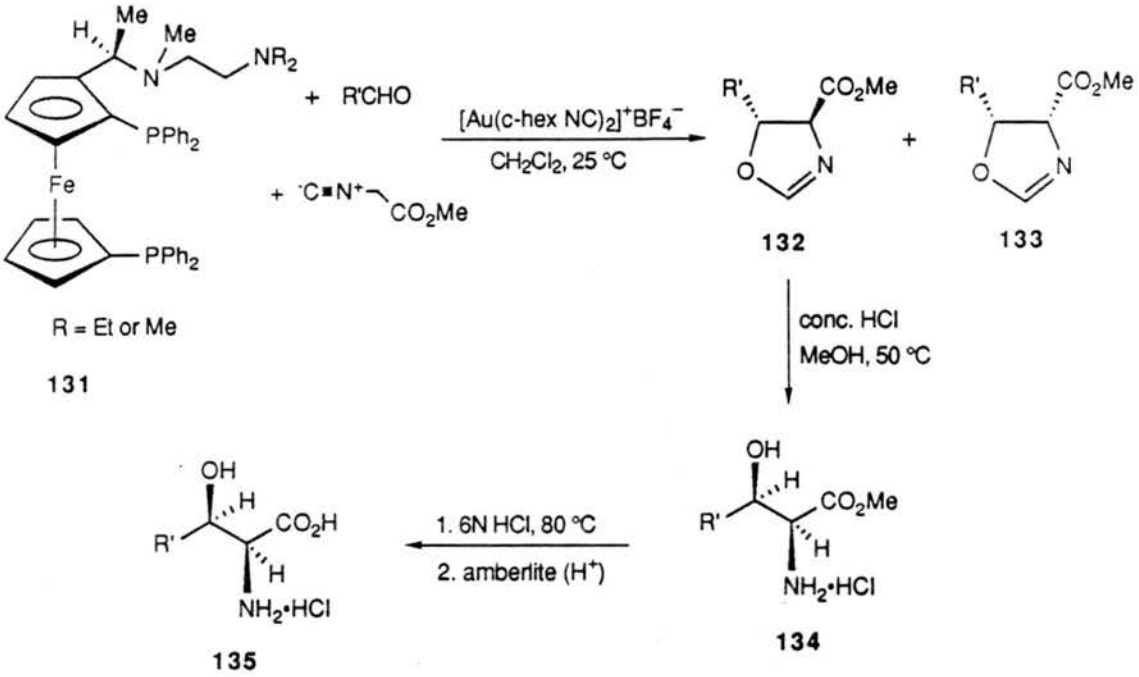
SCHEME 26



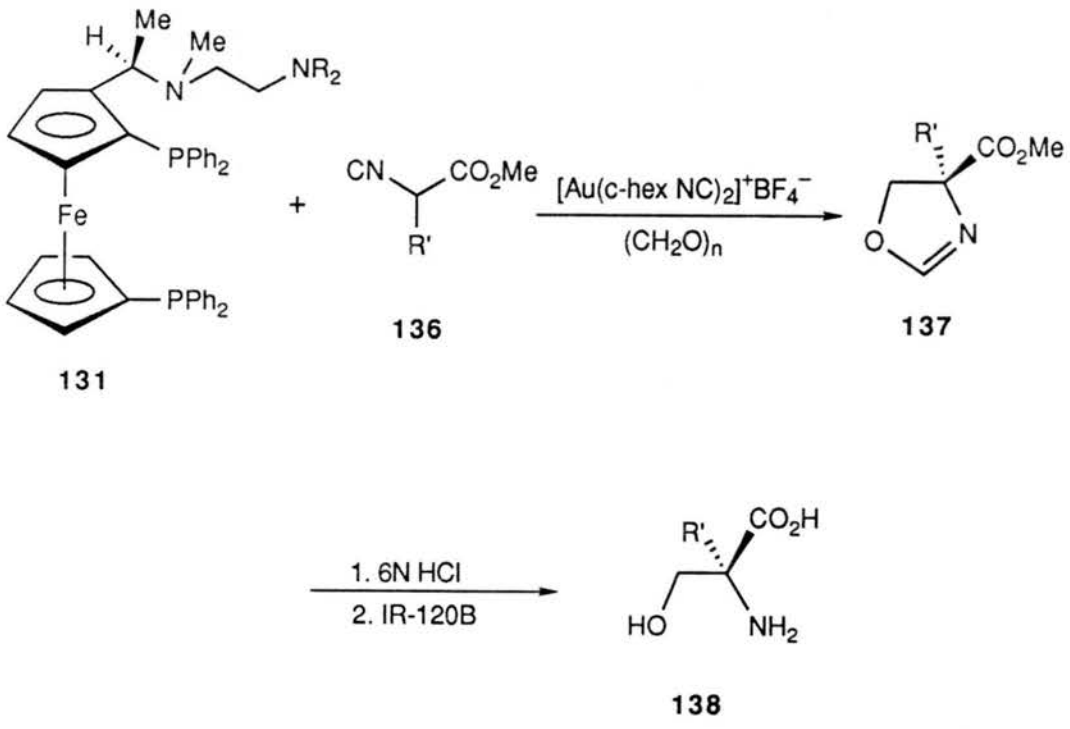
hydroxyacids and phenyl glycine (Scheme 25). The heterocycle **120** is converted into the mono-lactim ether **121** that undergoes enolate alkylation with several activated electrophiles furnishing the homologated systems **122** in excellent yields and good to excellent diastereoselectivities (49->95% de). The oxazinone can be cleaved with mild acid treatment to furnish the α-alkylated phenylglycine derivatives **123** which must be separated from the chiral auxilliary **124**. A strictly analogous system was reported[40] utilizing 2-furylglycine (**126**) as the amino acid template (Scheme 26). Following the exact same route as that above, the α-alkylated-2-furyl glycines (**130**) are obtained *via* alkylation of the oxazinone **128**.

Hayashi, Ito and coworkers[41] have discovered an extremely interesting catalytic asymmetric aldol condensation between aldehydes and methyl isocyanoacetate employing an optically active gold(I) complex. As shown in Scheme 27, the ferrocenyl ligand (**131**) is admixed with a gold(I) salt and methyl isocyanoacetate in CH_2Cl_2, followed by addition of the aldehyde. After reaction at ambient temperature for 20 h, the oxazolines **132** and **133** were isolated by bulb-to-bulb distillation. The reaction shows selectivity for the *trans*-isomers (>80:<20) with enantiomeric excesses ranging from 72-97%. The *cis*-isomers, on the other hand are obtained in mediocre or poor optical purity. Compounds **132** are converted in high yield to the *threo*-β-alkyl serine derivative **135** by hydrolysis with concentrated HCl at 50 °C and subsequent hydrolysis of the methyl ester and ion-exchange chromatography. In subsequent communications,[42] the same group reported on the condensation of formaldehyde with substituted methyl isocyanoacetates (**136**) using the same catalyst **131** (Scheme 28). As above, the aldol condensation proceeds in a stereoselective manner with incipient trapping of the initial aldol on the isocyanate to furnish the oxazolines **137** as the isolated products. The

SCHEME 27



SCHEME 28

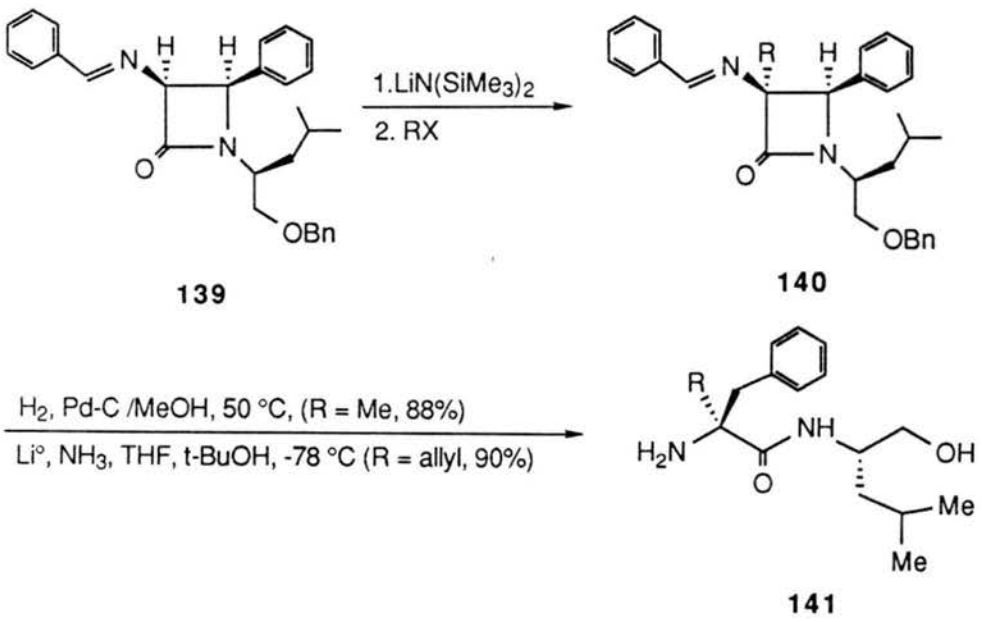


chemical yields for the formation of **137** are excellent, but the enantiomeric excess is somewhat modest ranging from 44-81%. Hydrolysis of the

oxazoline is performed with 6N HCl followed by ion-exchange chromatographic elution of the α-alkylated serine derivatives **138**.

Ojima and associates[43] have developed a clever and potentially quite useful way to make various optically active amino acids and peptide derivatives through stereoselective alkylations of β-lactams. The overall strategy is predicted on the use of 4-phenyl-substituted β-lactams which can be reductively cleaved at the N-1/C-4 (benzylic) bond to produce the corresponding phenylalanine-containing amino acid or peptide. As shown in Scheme 29, the benzylidene Schiff base of a 3-amino-4-phenyl β-lactam **139** is metallated with lithium bis(trimethylsilyl)amide, followed by treatment with alkyl halide to give the adducts **140**. Alkylation occurs in a stereoselective manner anti- to the 4-phenyl substituent. Hydrogenolysis in the case of R = Me or Birch reduction in the case of R = allyl provides the α-alkylated phenyl alanine peptides to leucinol **141** in high yield as virtually optically pure substances.

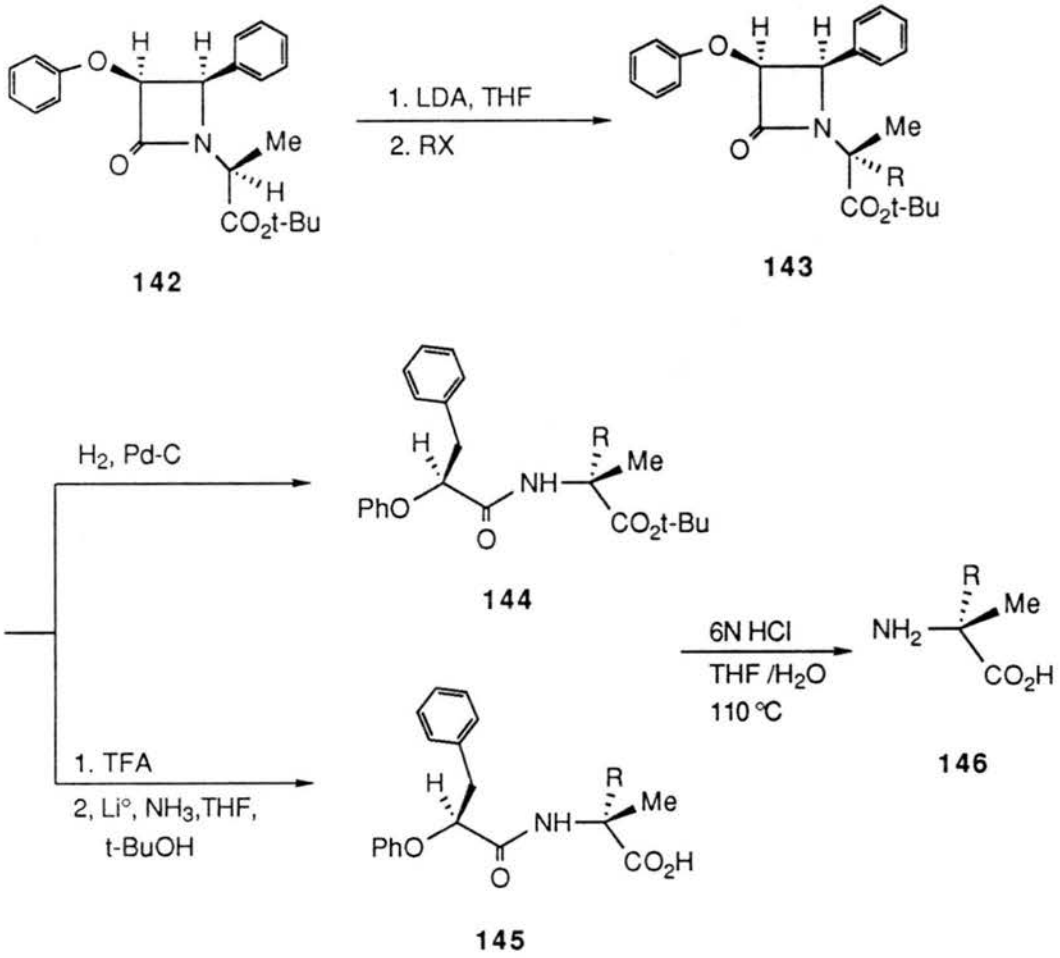
SCHEME 29



139 **140** **141**

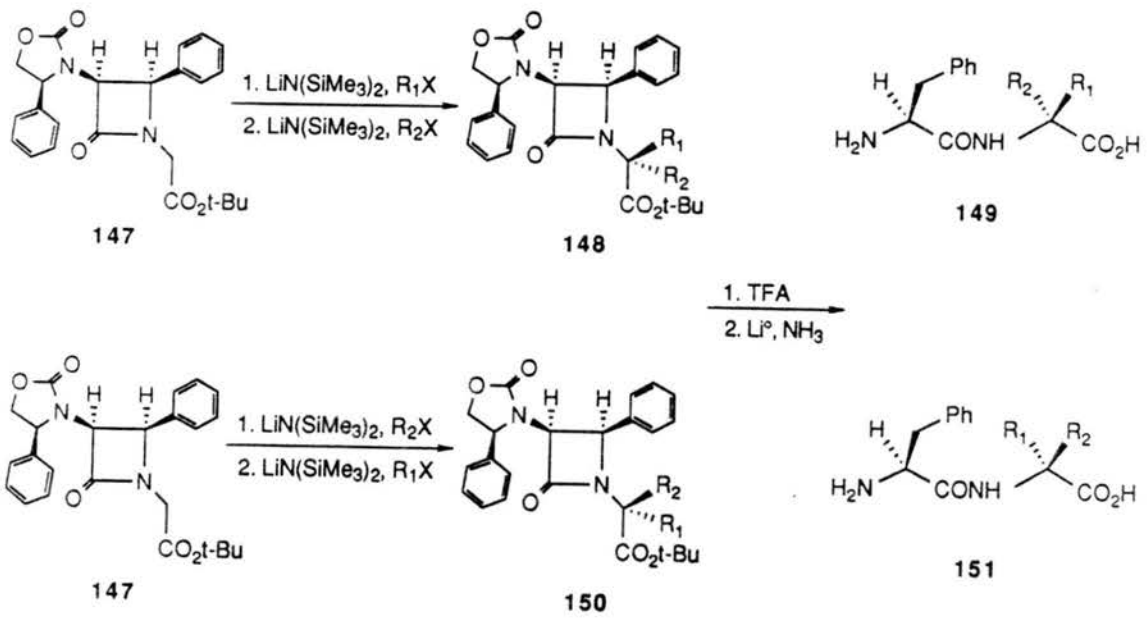
In a related series of investigations, Ojima and Qiu[44] reported on the stereoselective alkylations of amino acid residues incorporated at N-1 of the β-lactam ring as shown in Scheme 30. Metallation of **142** and subsequent alkylation furnishes the anti- adducts to the C-4 phenyl moiety with a high degree of diastereoselectivity (93->98% de). Reductive cleavage can be performed to access either the t-butyl ester **144** or the acid **145**; either derivative can then be hydrolyzed completely to the α-alkylated amino acid **142** with 6N HCl at 110°. By applying this concept to the β-lactam glycinate **147**,[45] the sequential double alkylation provides the di-substituted glycinates

SCHEME 30



142 **143** **144** **145** **146**

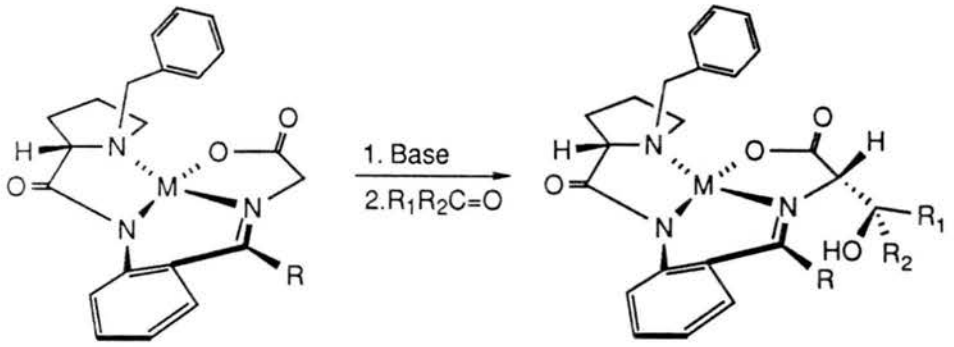
SCHEME 31



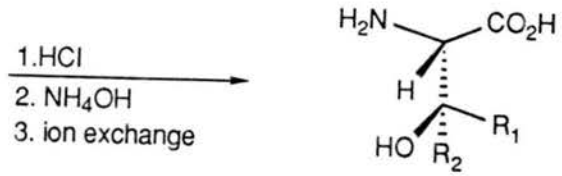
148 in high yield and optical purity (>99% de). The homologated glycinates **150** can be obtained by changing the order of addition of the two alkyl halides. The sequential deprotection of the t-butyl group and dissolving metal reduction give the corresponding phenylalanine dipeptide **149** and **151**, respectively (Scheme 31).

Belokon, et. al.,[46] have extensively developed an interesting and potentially quite useful enolate transition-metal (Ni or Cu) complexes of Schiff bases derived from glycine. The complex **152** is prepared by standard peptide coupling of N-benzyl-L-proline with *o*-aminoacetophenone (R = Me) and glycine followed by complexation to either Ni^{2+} or Cu^{2+}. The aldol condensations are then performed in the presence of a base under mild conditions to give the adducts **153** in good yields. The carbonyl component approaches primarily *anti*- to the N-benzyl group and the aldol stereoselection greatly favors the *threo*- configuration. The diastereomeric complexes can be separated by chromatography in stereochemically pure form, and hydrolyzed

SCHEME 32

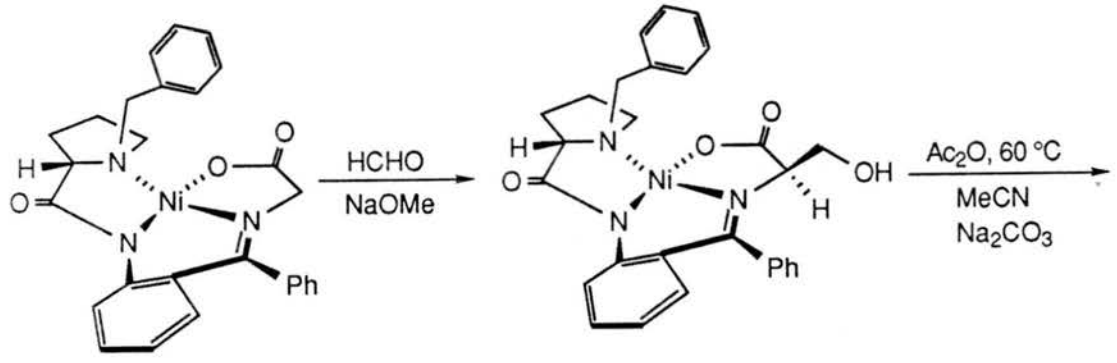


152 153

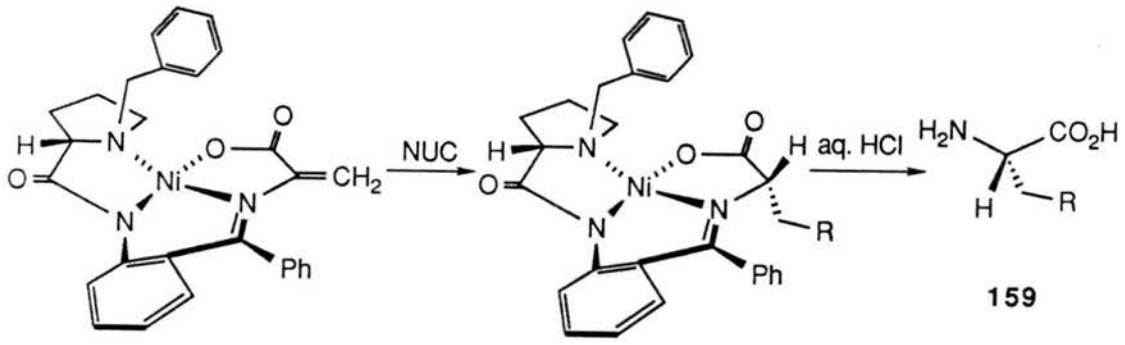


154

SCHEME 33

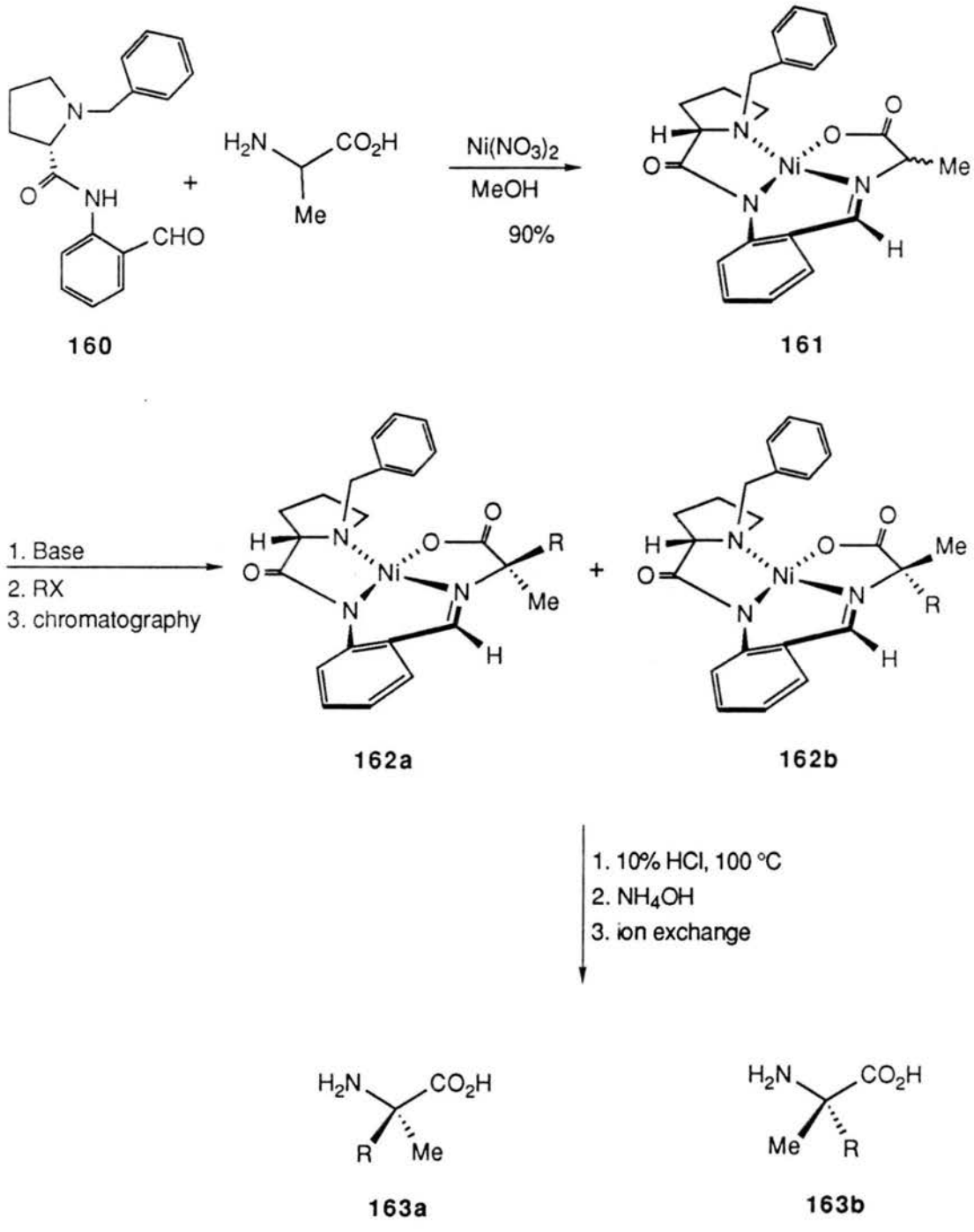


155 156



157 158 159

SCHEME 34



160 **161** **162a** **162b** **163a** **163b**

to the free amino acids with 70-96% ee's. The chiral complex can be recovered in good to excellent yields (60-90%).

In a related study,[47] the dehydroalanine substrate **157** was prepared from the formaldehyde adduct (**156**) derived from **155** (Scheme 33). This

material proved to be a reactive Michael acceptor for a variety of nucleophiles. The thermodynamically most stable *anti-* isomers **158** are formed and hydrolyzed as above to the free amino acids **159** in moderate to high % ee's (50-98%).

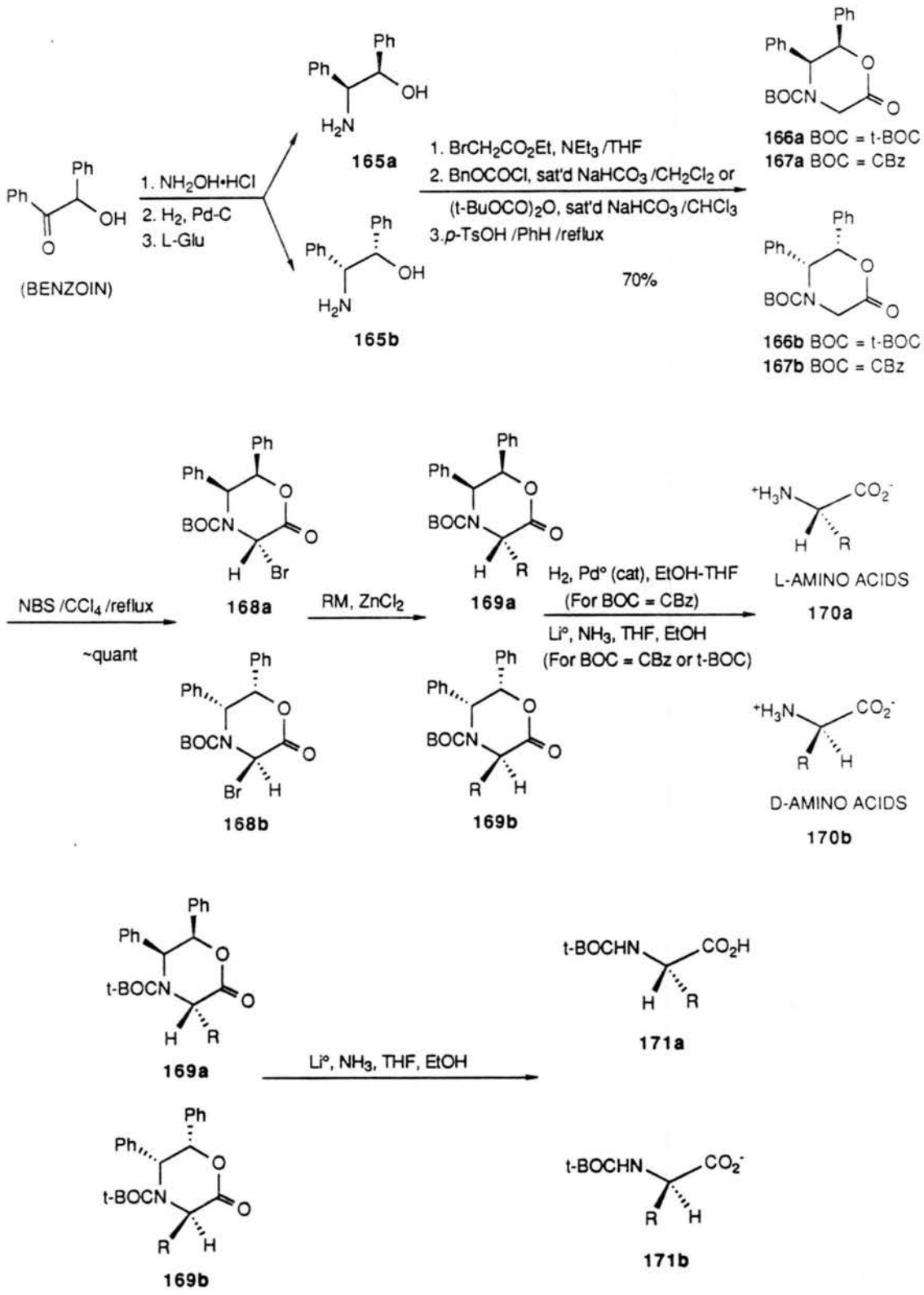
Alkylations[48] of the Ala complex **161** (Scheme 34) with reactive alkylating reagents furnished the corresponding α-alkylated alanine derivatives (**163**) after hydrolysis. The % de's in these reactions were not very good, but separation of the pure diastereomeric complexes (**162a/b**) by silica gel chromatography followed by hydrolysis gave enantiomerically pure amino acids (**163**).

The preceding survey, given in order to demonstrate the intense effort being expended in the area of asymmetric amino acid synthesis utilizing chiral glycine enolate equivalents, is necessarily brief. In many cases, the factors controlling stereochemistry were not discussed. While several elegant and general methodologies to optically active amino acids have emerged there is still plenty of room for more practical and efficient alternatives. Williams and Sinclair, et. al. developed a general asymmetric synthesis of α-amino acids based on a heterocycle containing a latent electrophilic glycine equivalent. The ensuing paragraphs briefly review their works.

C. Erythro-5,6-Diphenyl-2,3,5,6-Tetrahydro-4H-1,4-Oxazin-2-Ones as Electrophilic Glycinates

The most extensively studied optically pure electrophilic glycine templates are prepared as shown in Scheme 35.[49] Inexpensive benzoin is converted into the oxime and stereospecifically hydrogenated to the racemic *erythro*-amino alcohols **165**; these are subsequently resolved through the agency of the derived L-glutamate salts according to Tishler, et. al.[50] on a large scale providing each optical isomer **165a** and **165b** of >99% ee. Each

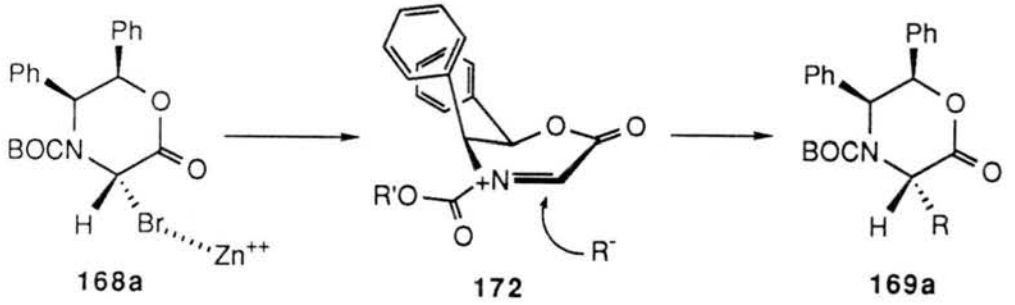
SCHEME 35

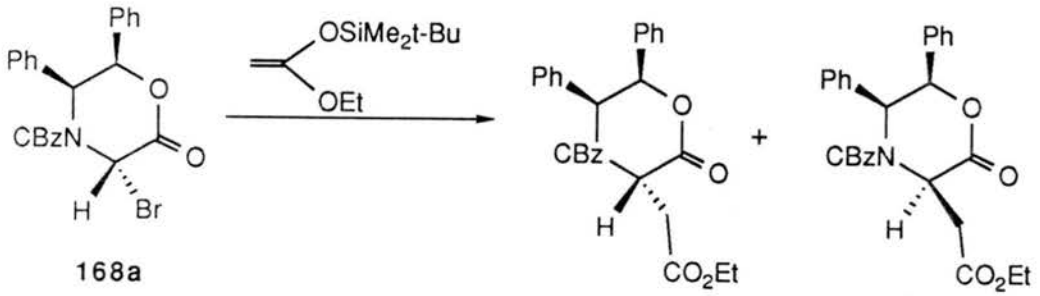

(BENZOIN)
1. NH2OH•HCl
2. H2, Pd-C
3. L-Glu
165a
165b
1. BrCH2CO2Et, NEt3 /THF
2. BnOCOCl, sat'd NaHCO3 /CH2Cl2 or
(t-BuOCO)2O, sat'd NaHCO3 /CHCl3
3. p-TsOH /PhH /reflux
70%
166a BOC = t-BOC
167a BOC = CBz
166b BOC = t-BOC
167b BOC = CBz
NBS /CCl4 /reflux
~quant
168a
168b
RM, ZnCl2
169a
169b
H2, Pd° (cat), EtOH-THF
(For BOC = CBz)
Li°, NH3, THF, EtOH
(For BOC = CBz or t-BOC)
L-AMINO ACIDS
170a
D-AMINO ACIDS
170b
169a
169b
Li°, NH3, THF, EtOH
171a
171b

isomer is then separately alkylated with ethyl bromoacetate; acylated with either benzylchloroformate or di-t-butyldicarbonate and; finally lactonized with catalytic *p*-TsOH in hot benzene or toluene to afford the crystalline lactones **166/167** in 70% overall yield from the amino alcohols. The entire sequence from benzoin is accomplished without any chromatographic separations. All four isomers **166a/166b**; **167a/167b** as well as the corresponding racemic substances are now commercially available.

Bromination of these oxazinones with NBS in refluxing carbon tetrachloride proceeds in essentially quantitative yield. The relative

SCHEME 36



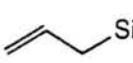
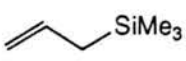
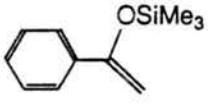
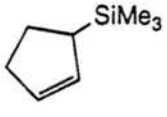
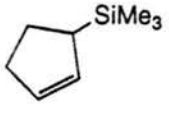
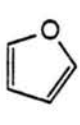
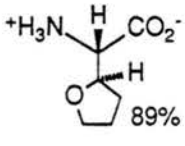
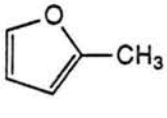
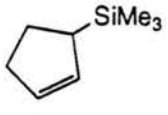


$ZnCl_2$	CH_2Cl_2	1	:	45
$ZnCl_2$	THF	1	:	14-45
AgOTf	THF	1	:	2

stereochemistry of the bromide is *anti-* and only a single diastereomer is produced in the reaction. Reaction of **168** with various organometallic reagents in the presence of zinc chloride results in displacement of the bromine providing the homologated oxazinones **169**. In most cases, the relative stereochemistry of the coupling reactions proceeds with net *retention* providing *anti*-**169**. The authors speculate that the zinc(II) salt coordinates to the bromine ultimately providing the reactive iminium species **172**. Since the phenyl rings are *cis*, the sterically least encumbered approach is from the face *anti-* to the two phenyl substituents. In the case of the ketene silyl acetal of ethyl acetate, the *syn*-isomer **173b** is obtained as the major product (Scheme 36). This result indicates that in the non-polar solvent methylene chloride and with a weak Lewis acid (zinc chloride), the electron-rich ketene silyl acetal effects a clean S_N2 displacement of the bromide. When the conditions are changed to encourage formation of the iminium species **172** (more polar solvent, strong halophile), more of the S_N1 product (*anti*) begins to appear.

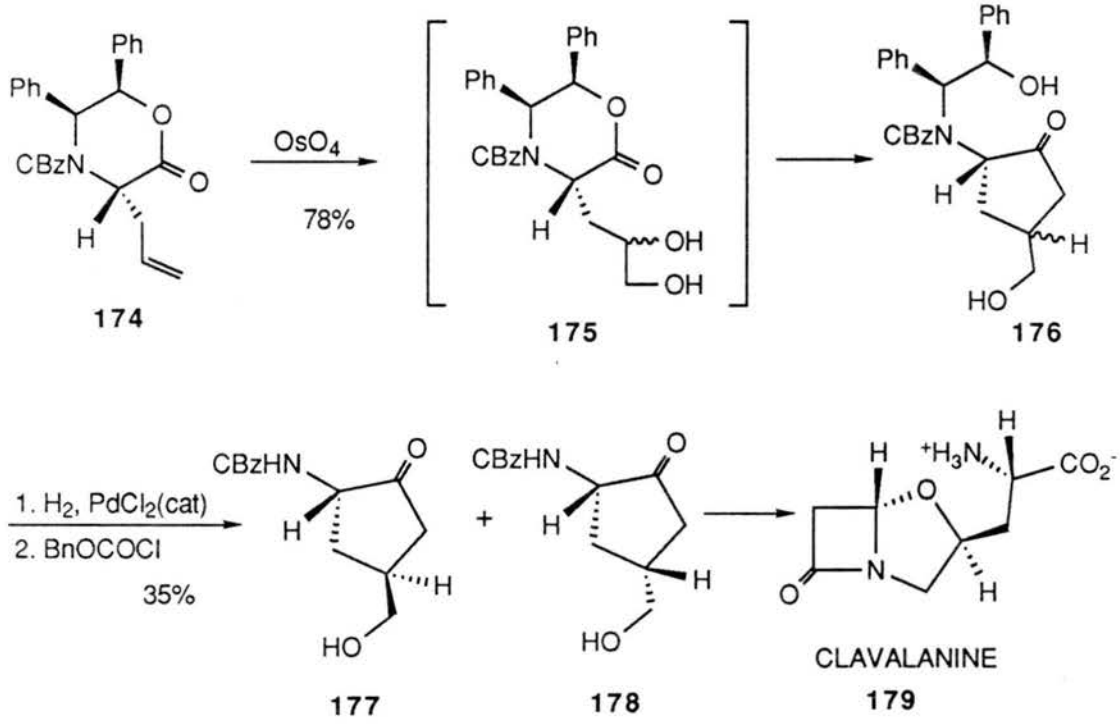
Depending on which type of BOC protecting group is employed, two different types of reductive protocol have been devised. In the case of the N-CBz systems, either catalytic hydrogenation on a Pd° catalyst or dissolving metal reduction directly provides the free zwitterionic amino acids **170**. In the corresponding N-t-BOC systems, dissolving metal reduction directly provides the N-t-BOC protected amino acids **171**. Table 1 lists the results of surveying a variety of coupling reactions with **168**, the coupling conditions, the reduction method, the amino acid produced in each case and the % ee. The chemical yields for **169** reflect the two step conversion of the oxazinones **166/167** into the bromides **168** and hence to **169**. The % ee's are excellent, typically exceeding 96% ee.

TABLE 1

BOC GROUP	NUCLEOPHILE	REACTION CONDITIONS	YIELD	DEPROTECTION METHOD	YIELD of AMINO ACID	%ee
CBz		$ZnCl_2$ /THF 25°C	74%	$H_2/PdCl_2$ (cat) EtOH, 20psi	85% ETHYLASPARTATE	> 96%
		$ZnCl_2$ /THF 25°C	66%	$H_2/PdCl_2$ (cat) EtOH, 20psi	93% NORVALINE	>98%
		$ZnCl_2$ /THF 25°C	66%	Li^o /NH_3 /EtOH	90% ALLYLGLYCINE	>91%
	H_3CZnCl	THF /-78°C	46%	$H_2/PdCl_2$ (cat) EtOH, 20psi	100% ALANINE	>96%
	Bu_2Cu (CN) Li	THF /Et_2O -78°C	48%	$H_2/PdCl_2$ (cat) EtOH, 20psi	52% NORLEUCINE	>99%
		$ZnCl_2$ (cat) CH_3CN /25°C	72%	$H_2/PdCl_2$ (cat) EtOH, 20psi	91% HOMOPHENYLALANINE	>96%
		$ZnCl_2$ /THF 25°C	82%	$H_2/PdCl_2$ (cat) EtOH, 20psi	91% CYCLOPENTYLGLYCINE	>96%
		$ZnCl_2$ /THF 25°C	82%	Li^o /NH_3 /EtOH	94% CYCLOPENTENYLGLYCINE	>96%
		$ZnCl_2$ /THF 25°C	64%	$H_2/PdCl_2$ (cat) EtOH, 20psi	 89%	>96%
		$ZnCl_2$ /THF 25°C	66%	$H_2/PdCl_2$ (cat) EtOH, 20psi	89% DIHYDROFURANOMYCIN	not determ.
t-BOC		$ZnCl_2$ /THF 25°C	63%	Li^o /NH_3 /EtOH	70% N-t-BOCALLYLGLYCINE	>96%
		$ZnCl_2$ /THF 25°C	59%	Li^o /NH_3 /EtOH	70% N-t-BOC-CYCLOPENTENYLGLYCINE	>95%

Several illustrations of the complementary utility of these systems to the enolate-based approaches are provided in Schemes 37-39. As shown in Scheme 37, the crystalline allylated substance **174** was osmylated to provide the γ-butyrolactones **176** as a 1:1 diastereomeric mixture in 78% yield. The initially formed diol **175** spontaneously rearranges to the thermodynamically more stable γ-butyrolactone isomer under the reaction conditions. Reductive removal of the chiral auxiliary, followed by acylation with benzyl chloroformate provided **177** and **178** which were separated by silica gel chromatography. Isomer **178** was previously converted into the unusual β-lactam antibiotic clavalanine (**179**) by a Hoffman-LaRoche group; the Roche synthesis of **179** is a multi-step preparation from D-xylose. Although the oxidation of **174** proceeds without stereocontrol, the brevity of the approach remains an attractive element of functionalizing a derivatized oxazinone such as **174**.

SCHEME 37

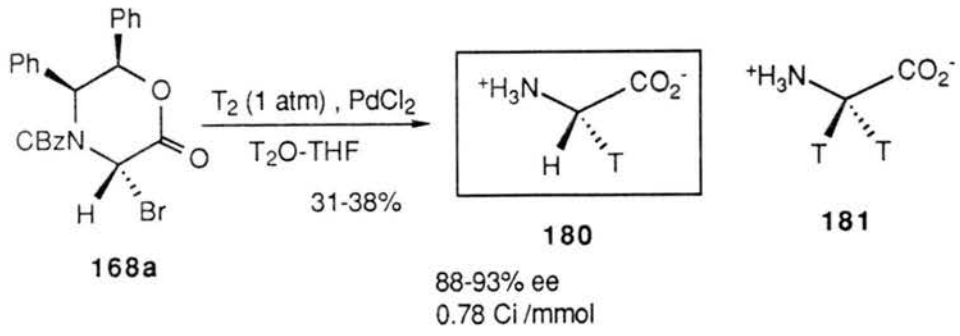


Scheme 38 details an extremely short and convenient synthesis of chiral glycine derivatives.[51] The bromide **168a** is simply reduced with tritium carrier gas on Pd° at 1 atmosphere in tritiated water/THF. Ion-exchange isolation provided **180** in 31-38% chemical yields that was 88~93% optically pure and had a specific activity of 0.78 Ci/mmol. The corresponding α-deuterio glycines[52] were obtained by hydrogenating **168a** or **168b** on a Pd° catalyst in D_2O giving material of 84-90% isotopic purity, 77-82% ee and 54% yield.

Scheme 39 demonstrates an asymmetric synthesis[53] of the recently discovered amino acid β-carboxy aspartic acid (Asa, **183**) that was obtained from ribosomal protein hydrolysates by Koch, et. al. Asa is a notoriously unstable amino acid that is sensitive to decarboxylation under acidic conditions and elimination of ammonia under basic conditions. The inherent lability of Asa is sufficiently problematical in that the harsh conditions employed in conventional peptide-sequencing techniques (resulting in production of Asp in most cases) have limited the detection of Asa in natural systems. Coupling of **168a** with sodium dibenzyl malonate in THF furnished in 53% yield, the malonate **182** as a 5.6:1, *syn:anti* mixture of diastereomers that was separated by chromatography. Reduction of all five benzylic residues over a Pd° catalyst provided Asa (**183**) as a 4:1 mixture with Asp. These were easily separated by acidic ion-exchange chromatography which allows Asa (pka = 0.8) to pass freely off the column. The pure Asa is obtained in 30% yield from **182** and >98% ee.

A very useful coupling reaction has been developed by Williams and Zhai[54] as shown in Scheme 40. The oxazinones are brominated in the usual way and then condensed with trialkyl tin acetylides in the presence of zinc chloride in refluxing CCl_4 to afford the crystalline alkynes **184** as single *anti-*

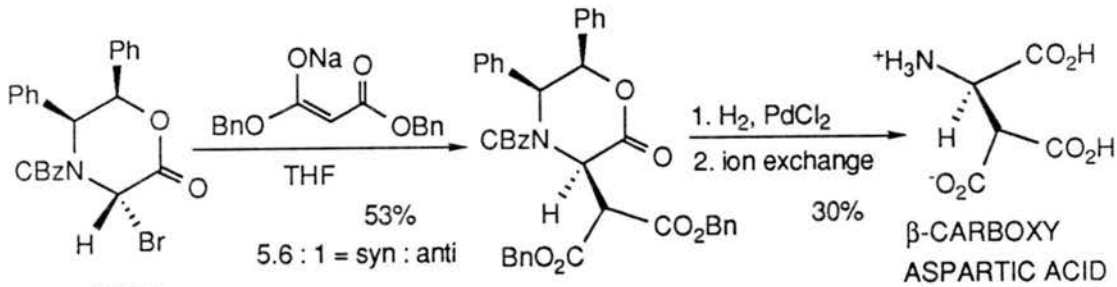
SCHEME 38



168a **180** **181**

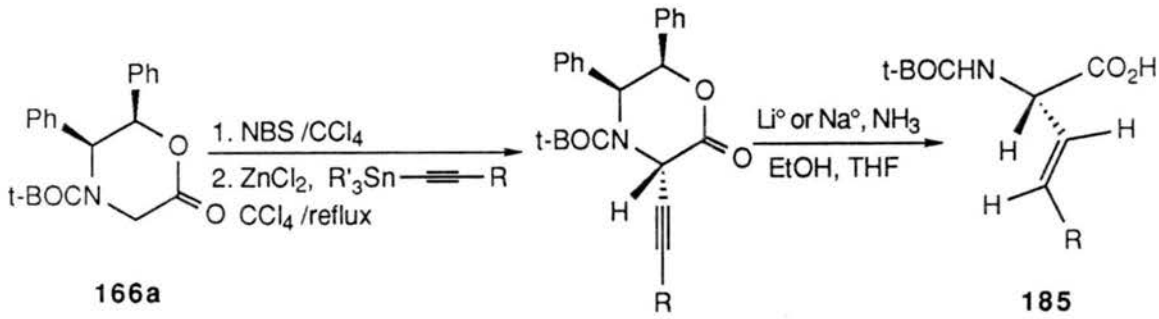
88-93% ee
0.78 Ci /mmol

SCHEME 39



168a **182** **183** (Asa)

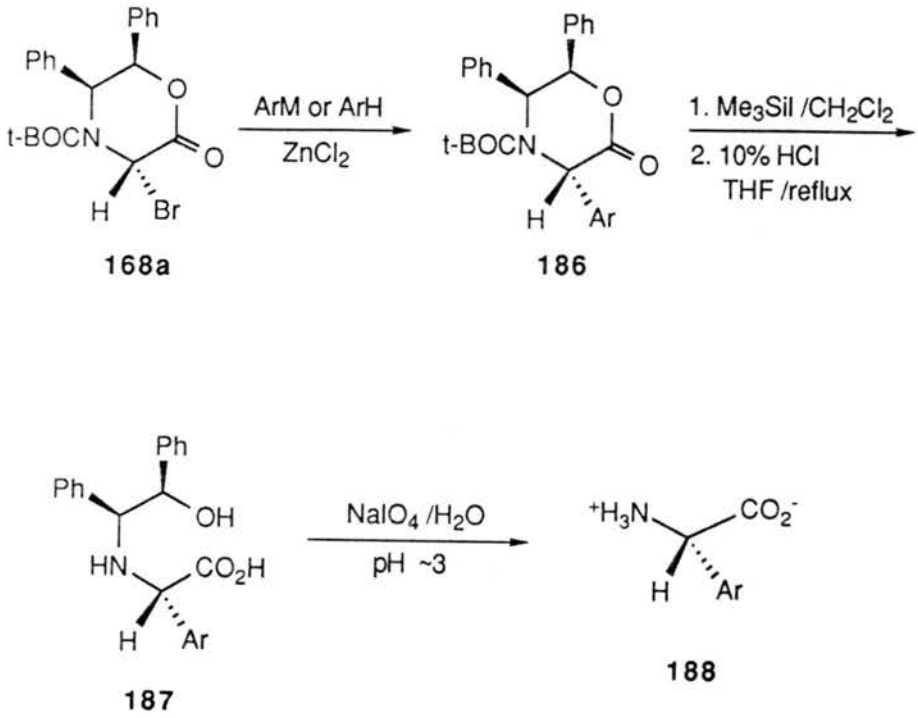
SCHEME 40



166a **184** **185**

diastereomers. Dissolving metal reduction directly provides exclusively the E-vinyl glycine derivatives **185** in good chemical yields and good to excellent % ee's (65->98%). The partial racemization occurs during the reduction step, the subsequent work-up or % ee determination since the alkynes **181** are stereochemically pure (>99% de and >99% ee).

SCHEME 41



168a **186** **187** **188**

Williams and Hendrix[55] have also studied that the bromide **168a** undergoes stereoselective reactions with aryl cuprates and electron-rich aromatic compounds under Friedel-Crafts conditions as shown in Scheme 41. Unlike all of the homologated substances discussed above, the adducts **186** are subject to reductive cleavage at the Ar-C-N linkage and therefore requires an alternate protocol for removing the chiral auxiliary in accessing the difficult, racemization-prone α-aryl glycines. Employing the method of Weineges[56] used on a related oxazinone, the lactones **186** are treated with trimethylsilyl iodide to remove the t-BOC group and then hydrolyzed in hot aqueous HCl to afford the hydroxy acids **187**. Treatment of these crude substances with sodium periodate in (pH 3) aqueous THF, followed by ion-exchange purification, furnishes the free amino acids **188** in good overall yields and good to excellent % ee's (82-94%).

The oxazinones **166** and **167** were anticipated to function as versatile glycine carbanions to afford the homologated lactones **169**. Unfortunately, numerous attempts at generating the enolate anions from **166** and **167** (LDA; THF; -100°~-78°C; NaH; KOt-Bu; etc.) resulted in instantaneous decomposition and no detectable alkylation or deuteration products being isolable.[57] We have now found[58] that lithium or sodium bis(trimethyl)silyl amide in THF at low temperature effects the clean deprotonation of these substrates without the significant decomposition accompanied by the other bases examined. The results of these studies are presented in the following chapters.

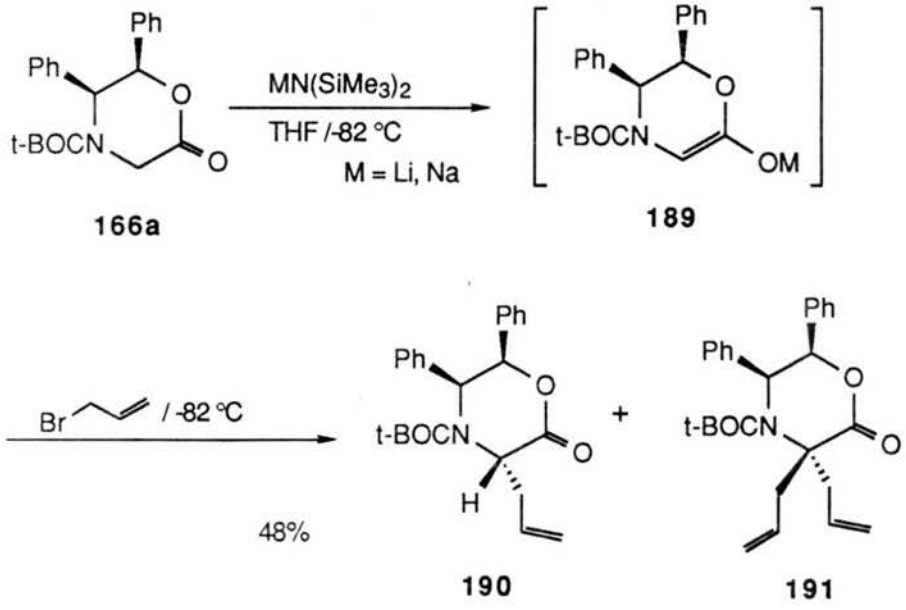
CHAPTER 2

ERYTHRO-5,6-DIPHENYL-2,3,5,6-TETRAHYDRO-4H-1,4-OXAZIN-2-ONES AS NUCLEOPHILIC GLYCINATES

A. Synthesis of α-Amino Acids

The enolate alkylation of the oxazinone **166a** with allyl bromide was first examined as shown in Scheme 42. In a preliminary attempt, the enolate **189** was generated with 1 equivalent of lithium bis(trimethylsilyl)amide in THF at -82 °C for 70 min and then treated with allyl bromide. After reacting for 1 hr, standard aqueous work-up furnished the crystalline allylated lactone **190**, but in disappointingly low yield (~20%). The ^{1}H NMR spectrum of **190** in high

SCHEME 42



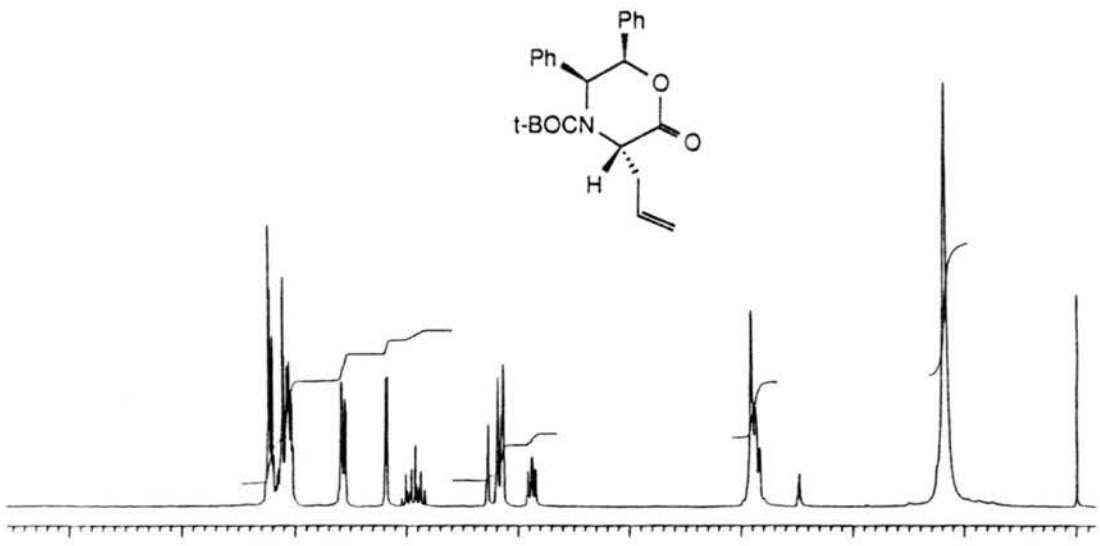
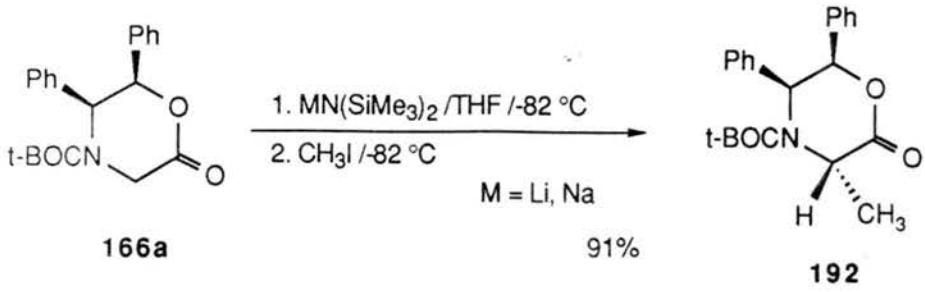


FIGURE 1 ^{1}H NMR of **190** in DMSO-d_6 at 393 °K

temperature (393°K) indicated that only one diastereomer had been formed (Figure 1). Comparison with the literature[49] proved that the relative stereochemistry of the allyl group at C-3 is *anti*- to the two phenyl rings. The employment of 2 equivalents of lithium bis(trimethylsilyl)amide and the generation of the enolate for 40 min furnished **190** in 71% yield and an unidentified product (12%) which proved to be the diallylated oxazinone **191**. The coupling reaction was remarkably clean. The enolate alkylation was also examined by employing sodium bis(trimethylsilyl)amide which had a more reactive counter ion than lithium. The displacement of allyl bromide by the enolate generated using 1 equivalent of sodium bis(trimethylsilyl)amide provided **190** in 48% yield and the unreacted oxazinone **166a** (21%). When allyl iodide was used instead of allyl bromide, TLC analysis showed that a significant amount of the diallylated product **191** was formed.

Next, the coupling reaction of the oxazinone **166a** with methyl iodide was examined. As shown in Scheme 43, the oxazinone **166a** was treated with 1.8 equiv. of lithium bis(trimethylsilyl)amide and subsequently methyl

SCHEME 43



166a **192**

iodide to give the crystalline methylated oxazinone **192** in 86% yield. The dimethylated lactone was not detected. Analysis of the ^{1}H NMR spectrum of **192** again showed that exclusively one diastereomer had been obtained (Figure 2). The employment of 1.1 equiv. of sodium bis(trimethylsilyl)amide also produced **192** in excellent yield (91%). These results were encouraging and the deprotection of the oxazinone auxilliary was now examined.

As previously reported by Williams and Sinclair, et. al.,[49] the homologated oxazinones **190** and **192** were subjected to dissolving-metal

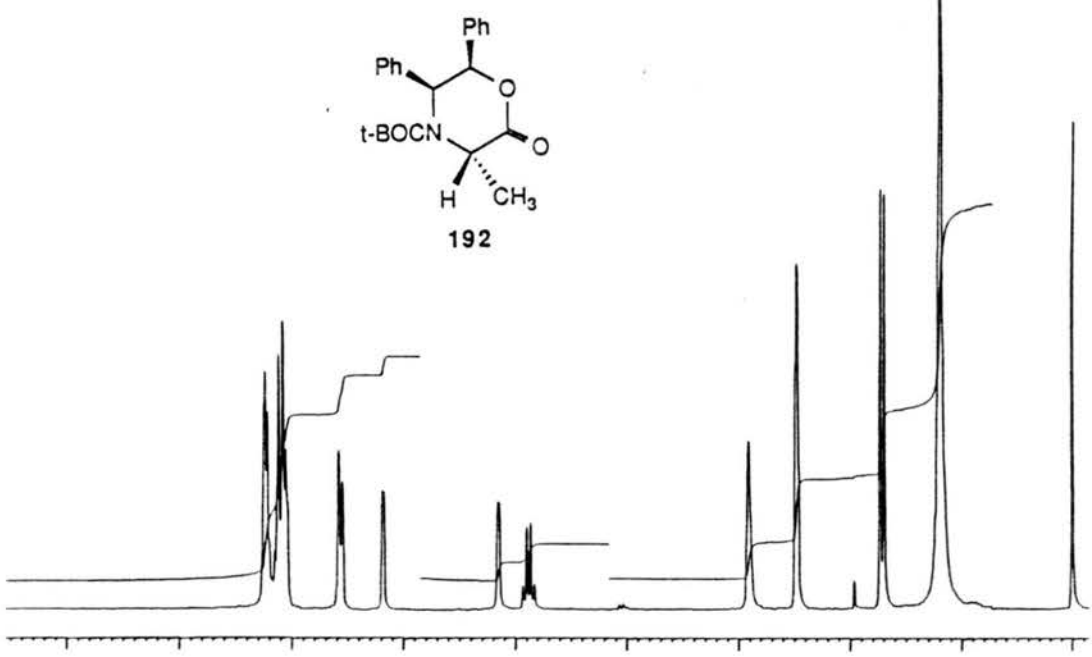
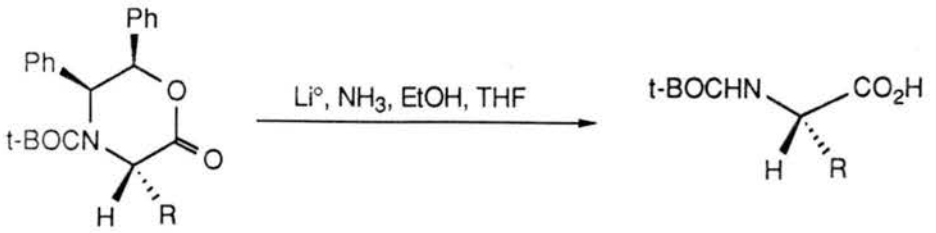


FIGURE 2 ^{1}H NMR of **192** in DMSO-d_6 at 393 °K

SCHEME 44



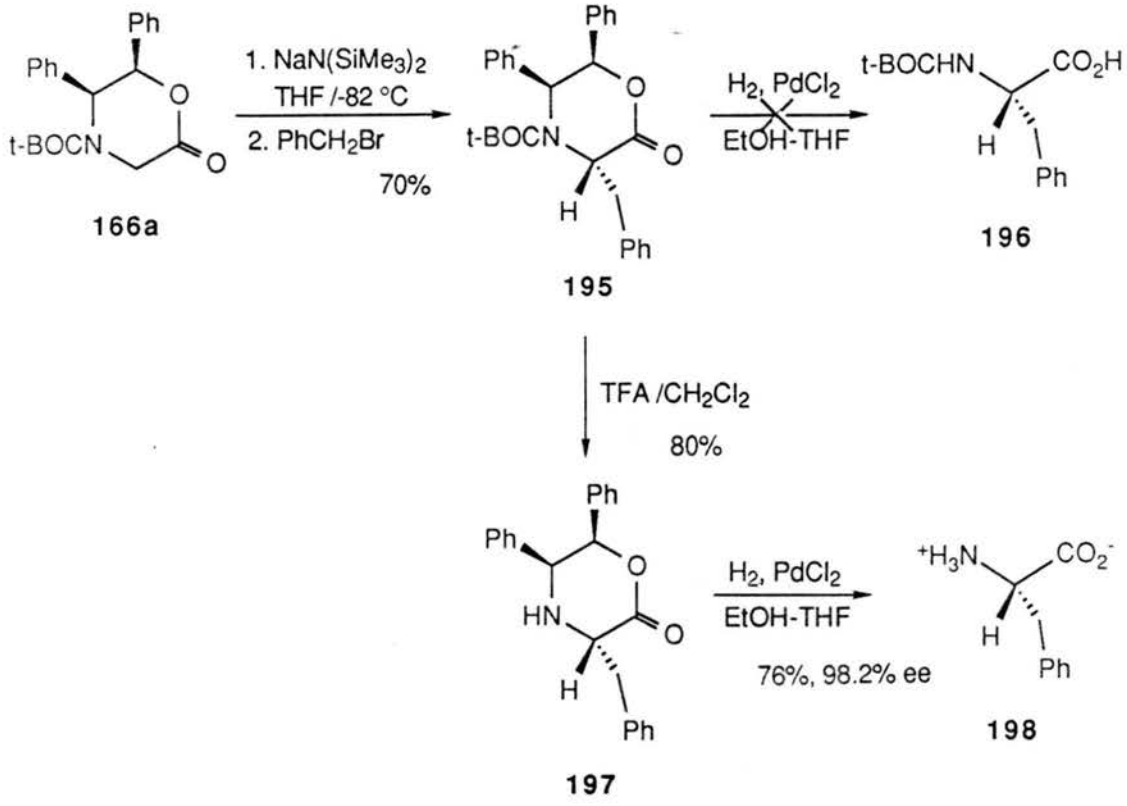
190 R = allyl
192 R = CH_3

50%, 98% ee **193** R = allyl
54%, 97.2% ee **194** R = CH_3

reduction (Scheme 44). As expected, the deblocking reaction proceeded smoothly to afford the t-BOC protected amino acids **193** and **194** in good yields, respectively. In both cases, excellent % ee's (98% for allyl; 97.2% for Me) were obtained and both optically active amino acids proved to have the L-(2S) configuration. These results support the hypothesis that the precursors **190/192** of the amino acids should have *anti-* relative stereochemistries.

Benzyl bromide was also examined as a coupling reagent. As shown in Scheme 45, treatment of **166a** with 1 equiv. sodium bis(trimethylsilyl)amide followed by addition of benzyl bromide produced the adduct **195** in good yield (70%) plus unreacted starting material **166a** (9%). In this case of dissolving metal-reducible functionality, hydrogenation over $PdCl_2$ catalyst was expected to directly give the t-BOC protected phenylalanine (**196**). Unfortunately, the hydrogenation conditions developed for the homologated CBz-lactones **169** by Williams and Sinclair[49] was not applicable to this system. This is presumably due to the requirement of a protonated benzylic amine as opposed to the less reactive benzylic urethane as a substrate for this reduction. The deprotection of t-BOC group by TFA readily provided the free amine **197** which was hydrogenated at 42 psi for 29 hours in the presence of $PdCl_2$ to afford the zwitterionic phenylalanine (**198**) in good yield (76%). Again, excellent enantiomeric excess (98.2%) was determined. The optical

SCHEME 45

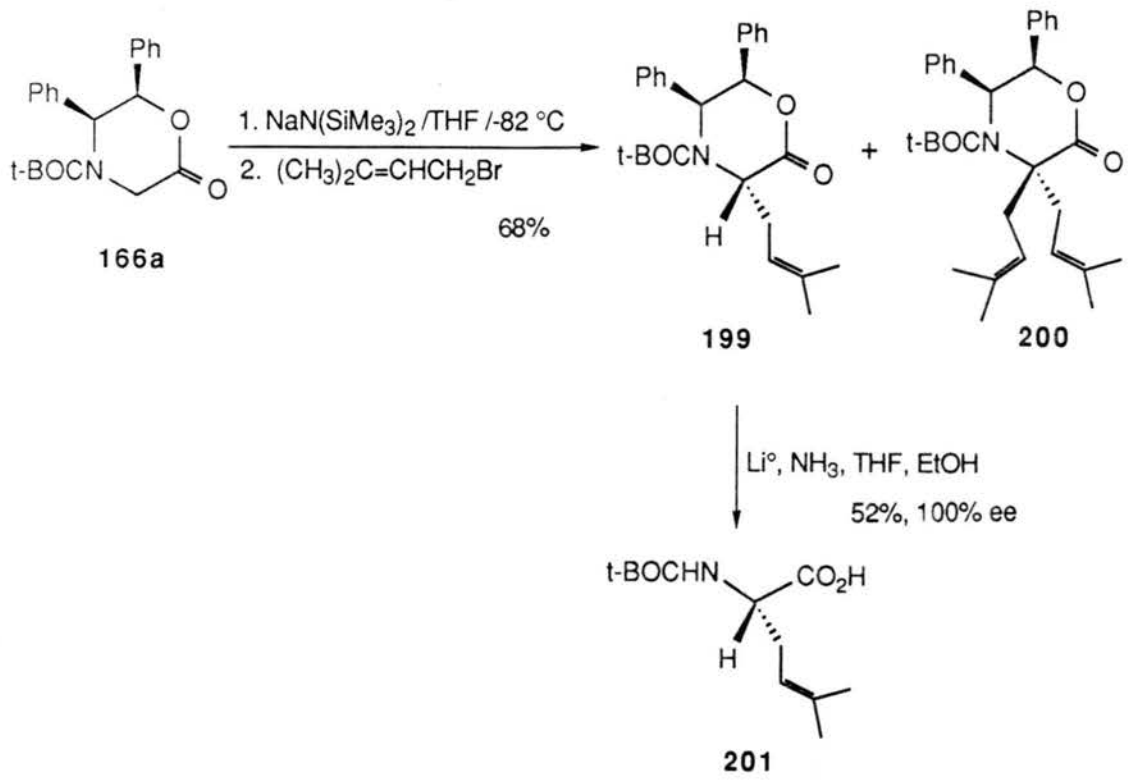


rotation indicated that the amino acid **198** possessed the L-(2S) configuration ($[\alpha]^{25}_D$ = -32° (c 0.1, H_2O); authentic $[\alpha]^{25}_D$ = -33.7° ~ -35.2° (c 2, H_2O)). This result confirms that the benzyl group of the lactone **195** should be *anti-* to the two phenyl rings.

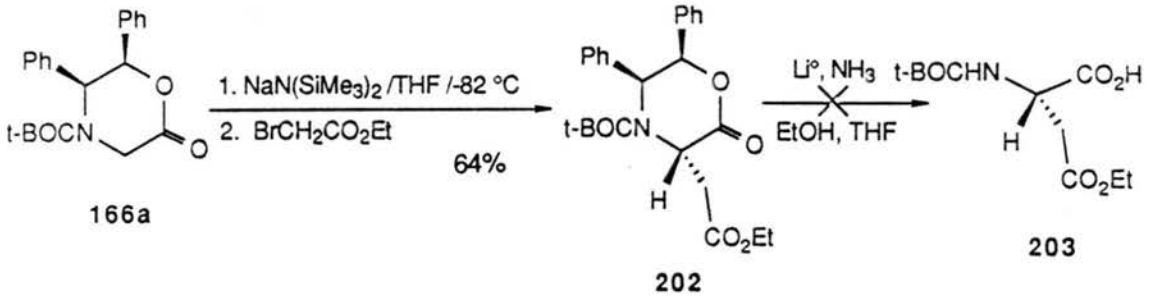
The enolate of **166a** underwent a smooth coupling reaction with dimethallyl bromide to furnish the *anti-* dimethallyl lactone **199**. Although 1 equiv. of sodium bis(trimethylsilyl)amide was used, a significant amount of the disubstituted oxazinone **200** was detected by TLC. Compound **199** was directly converted into the N-t-BOC protected dimethallyl glycine **201** as a pure enantiomer (100% ee) with L-(2R) configuration by the standard dissolving-metal reduction protocol (Scheme 46).

The enolate alkylation of **166a** with ethyl bromoacetate took place cleanly to provide the homologated *anti-* oxazinone **202** in 64% yield as

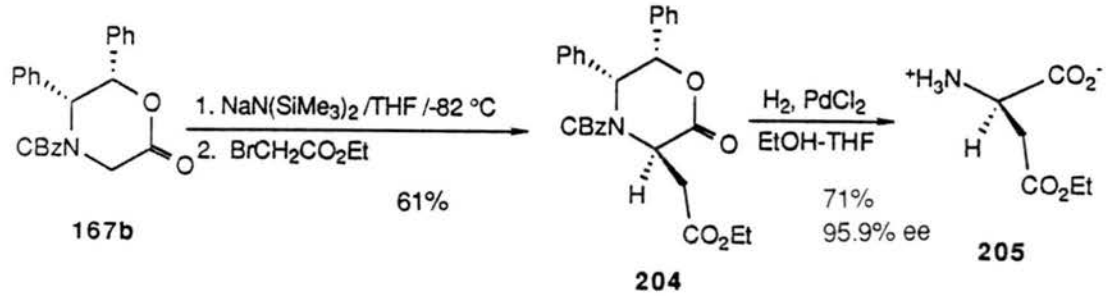
SCHEME 46



SCHEME 47



SCHEME 48



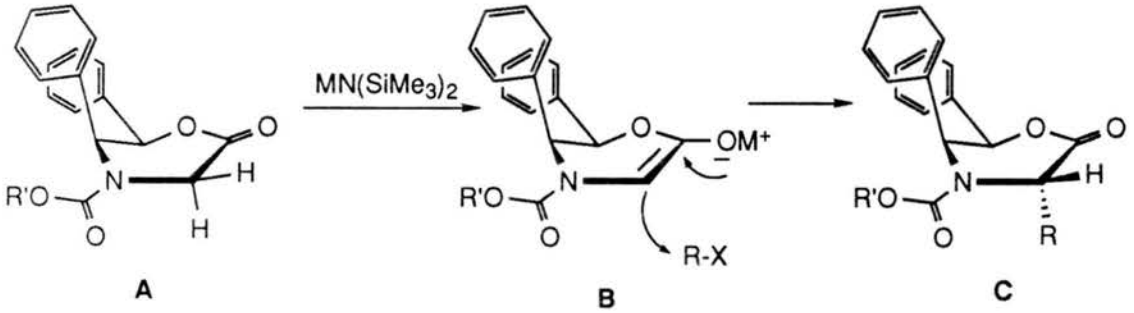
shown in Scheme 47. The standard dissolving-metal reduction to afford **203** was not successful, possibly due to overreduction of the ester functionality.

The N-CBz protected oxazinones **167a/b** were also anticipated to undergo enolate alkylation in the same manner as the t-BOC protected lactone **166a**. We first examined the enolate alkylation of the oxazinone **167b** (Scheme 48). Not surprisingly, generation of the enolate with sodium bis(trimethylsilyl)amide for 40 min at -82 °C and subsequent treatment with ethyl bromoacetate provided the *anti*- ethoxycarbonylmethyl oxazinone **204** in good yield. Catalytic hydrogenation over Pd° directly led to the zwitterionic, unnatural D-(2R) β-ethyl aspartic acid (**205**).

The stereochemistry of these enolate alkylations is readily rationalized by considering the conformer B that disposes the phenyl ring at C-5 in an axial 1,3-relation to the enolate carbon. As shown in Scheme 49, the electrophile approaches from the less hindered face providing the *anti*- oxazinone.

As already mentioned above, it turned out that the amino acids (allylglycine, alanine, phenylalanine and β-ethyl aspartic acid) have the L-stereochemistry as deduced from the stereochemistry of the corresponding precursor *anti*- oxazinones. In the case of the methallyl oxazinone, the relative

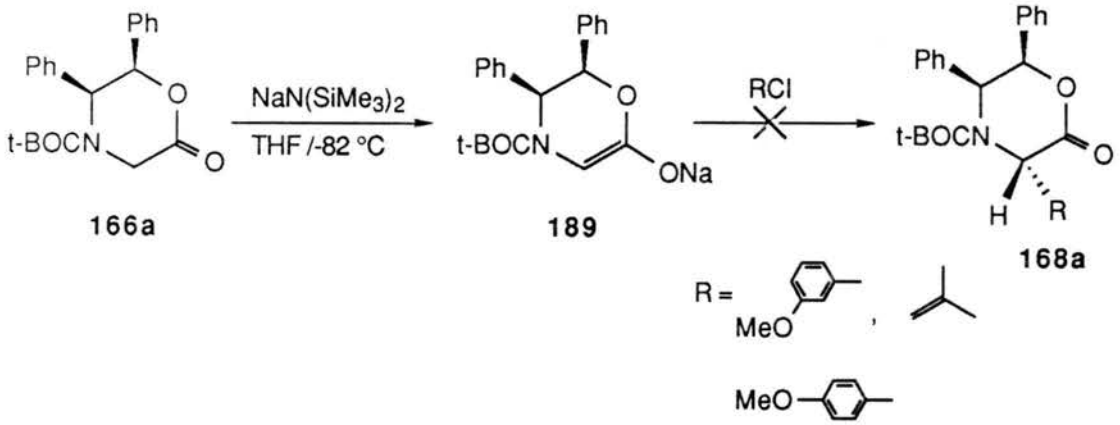
SCHEME 49



stereochemistry can be determined by two criteria[59] reported by Williams and Sinclair. The fact that the methallyl lactone **199** is nicely crystalline supports the empirical generalization that the oxazinone has the *anti-* relative stereochemistry. The $\Delta\delta$ value of the benzylic methine protons is 1.04, which is consistent with the range reported by Sinclair.

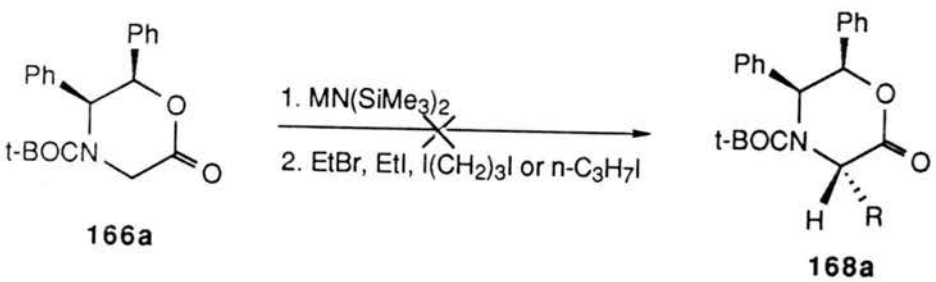
Next, we chose to examine less reactive electrophiles to attempt alkylation of the enolate. As shown in Scheme 50, the enolate alkylations with several activated alkyl chlorides were attempted. The alkylated lactones **168a** were not detected and only decomposition took place. Raising the temperature or adding solvating reagents, such as HMPA promoted decomposition of the enolate.

SCHEME 50



166a **189** **168a**

SCHEME 51



166a **168a**

TABLE 2

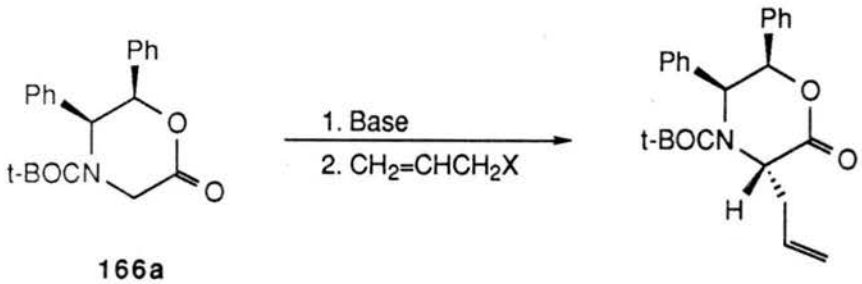
Entry	Oxazinone Substrate	Yield	RX	Base (equiv)	Amino Acid Yield	% ee
1	**166a**	20	CH_2=$CHCH_2Br$	$LiN(SiMe_3)_2$ (1)		
2	**166a**	71(12)[b]	CH_2=$CHCH_2Br$	$LiN(SiMe_3)_2$ (2)		
3	**166a**	48(21)[a]	CH_2=$CHCH_2Br$	$NaN(SiMe_3)_2$ (1)	50-70	98
4	**166a**	undeterm.	CH_2=$CHCH_2I$	$NaN(SiMe_3)_2$ (1)		
5	**166a**	86	CH_3I	$LiN(SiMe_3)_2$ (1.8)		
6	**166a**	91	CH_3I	$NaN(SiMe_3)_2$ (1.1)	54	97.2
7	**166a**	70(9)[a]	$PhCH_2Br$	$NaN(SiMe_3)_2$ (1)	76	98.2
8	**166a**	68(20)[a]	Me_2C=$CHCH_2Br$	$NaN(SiMe_3)_2$ (1)	52	100
9	**166a**	64	$BrCH_2CO_2Et$	$NaN(SiMe_3)_2$ (1.1)		
10	**167b**	61(20)[a]	$BrCH_2CO_2Et$	$NaN(SiMe_3)_2$ (1)	71	95.9
11	**166a**	0	*p*-MeO-$PhCH_2Cl$	$NaN(SiMe_3)_2$ (1)		
12	**166a**	0	*m*-MeO-$PhCH_2Cl$	$NaN(SiMe_3)_2$ (1)		
13	**166a**	0	CH_2=C(Me)CH_2Cl	$NaN(SiMe_3)_2$ (1)		
14	**166a**	0	CH_2=$CHCH_2CH_2Br$	$NaN(SiMe_3)_2$ (1)		
15	**166a**	0	EtBr	$LiN(SiMe_3)_2$ (1.8)		
16	**166a**	0	EtBr	$NaN(SiMe_3)_2$ (1)		
17	**166a**	0	EtBr	$KN(SiMe_3)_2$ (1)		
18	**166a**	0	EtI	$KN(SiMe_3)_2$ (2)		
19	**166a**	0	n-C_3H_7I	$NaN(SiMe_3)_2$ (1.2)		
20	**166a**	0	$I(CH_2)_3I$	$NaN(SiMe_3)_2$ (1.4)		

yield; a denotes recovered starting material
b denotes dialkylated product

We also examined unactivated alkyl halides as electrophiles. As shown in Scheme 51, unactivated alkyl bromide and iodides were not effective for the enolate alkylation. Table 2 summarizes the results discussed above.

In an effort to overcome this lack of reactivity, the effectiveness of several other bases was again studied. As shown in Scheme 52, the enolate alkylation of **166a** with allyl halides was examined; Table 3 lists the results. The alkylation with the less reactive bromide did not occur (entries 1 and 3).

SCHEME 52



166a **190**

TABLE 3

Entry	Base	X	Yield (%)
1	n-BuLi	Br	0
2	n-BuLi	I	8
3	LDA	Br	0
4	LDA	I	13
5	t-BuLi	I	38.4
6	NaH	I	16

Only decomposition took place or unreacted starting material was recovered. Treatment of the enolate with allyl iodide furnished the homologated lactone **190** but in disappointingly low yield. The best yield results from the most hindered and hence the least nucleophilic base (t-BuLi); hindrance: $LiN(SiMe_3)_2$ > t-BuLi > LDA > n-BuLi; nucleophilicity: $LiN(SiMe_3)_2$ < t-BuLi < LDA < n-BuLi. The fact that the enolate alkylation employing bases such as NaH, LDA and KOt-Bu mentioned in the introduction was not successful is obviously due to their nucleophilic character and subsequent decomposition of lactones (Eq. 7).

(eq 7)

As discussed above, this protocol is effective for the enolate alkylation exclusively with activated alkyl halides. With unactivated alkyl halides, unreacted starting material or substantial decomposition was observed under the standard conditions described above. In the case of some activated alkyl halides, a significant amount of disubstituted oxazinone was observed as a side product if more than 1 equiv. of base was employed. The dialkylated product was detected even with 1 equiv. of sodium bis(trimethylsilyl)amide. In the case of dimethallyl, allyl and benzyl bromide, significant amounts of dialkylated product was accompanied by significant amounts of unreacted starting material.

A simple and reliable protocol that obviates these problems was developed. It involves the addition of lithium or sodium bis(trimethylsilyl)amide to a solution of the oxazinone (**166/167**) containing the alkyl halide in THF at -78 °C. After standard aqueous work-up, this procedure furnished the α-

TABLE 4

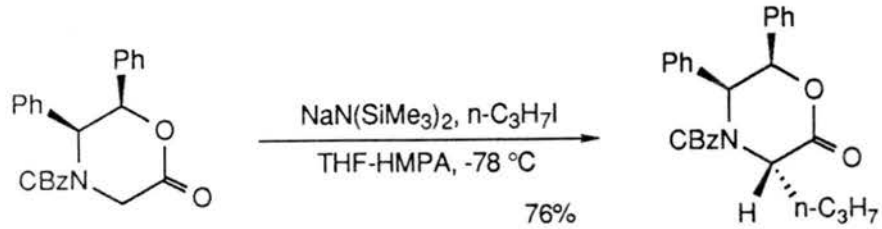
Entry	Oxazinone Substrate	RX	Base (equiv)		Yield
1	**167a**	n-C_3H_7I	$LiN(SiMe_3)_2$	(2)	47
2	**167a**	n-C_3H_7I	$NaN(SiMe_3)_2$	(2)	55
3	**167a**	n-C_3H_7I	$KN(SiMe_3)_2$	(2)	24(7)[b]
4	**167a**	n-C_3H_7I	$NaN(SiMe_3)_2$	(1)	36(34)[a]
5	**167a**	n-C_3H_7I	$NaN(SiMe_3)_2$	(1.5)	76(3)[a]
6	**167a**	n-C_3H_7I	$KN(SiMe_3)_2$	(1.5)	36(16)[b]
7	**166a**	n-C_3H_7I	$NaN(SiMe_3)_2$	(1.5)	77(12)[b]
8	**167a**	CH_3I	$NaN(SiMe_3)_2$	(1.5)	88
9	**166a**	CH_2=$CHCH_2I$	$LiN(SiMe_3)_2$	(1.2)	86(5)[a]
10	**167a**	CH_2=$CHCH_2I$	$LiN(SiMe_3)_2$	(1.2)	82
11	**166a**	Me_2C=$CHCH_2Br$	$NaN(SiMe_3)_2$	(1.1)	84
12	**167b**	$PhCH_2Br$	$NaN(SiMe_3)_2$	(1.2)	77(6)[b]

yield a denotes recovered starting material
b denotes dialkylated product

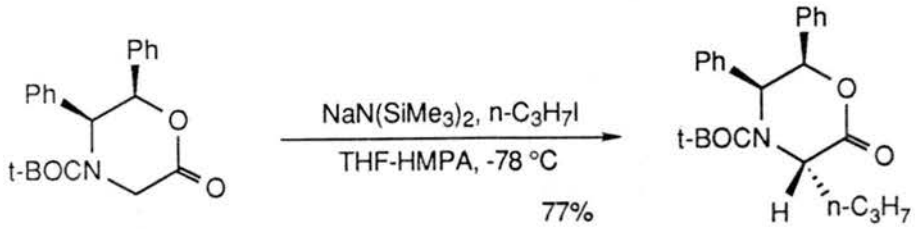
monosubstituted oxazinones in excellent yields. Table 4 shows the results.

As shown in Scheme 53, the enolate alkylation with unactivated n-propyl iodide took place smoothly to give the homologated lactone **206** in good yield. The use of HMPA as cosolvent (THF:HMPA = 10:1) substantially increases the yield. The best base is sodium bis(trimethylsilyl)amide and 1.5 equiv. was found to be the optimal stoichiometry (Table 4, entry 5). Potassium bis(trimethylsilyl)amide is too reactive for efficient monoalkylation resulting in decomposition and also gives rise to undesired disubstituted product (Table 4, entries 3 and 6). By employing the same method, the t-BOC lactone **166a** was converted to the n-propyl oxazinone **207** in 77% yield.

SCHEME 53

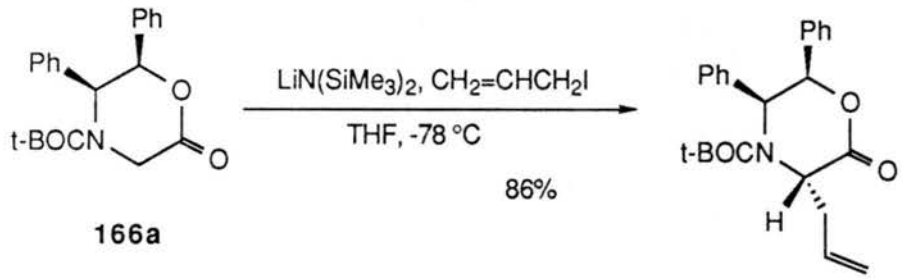


167a **206**

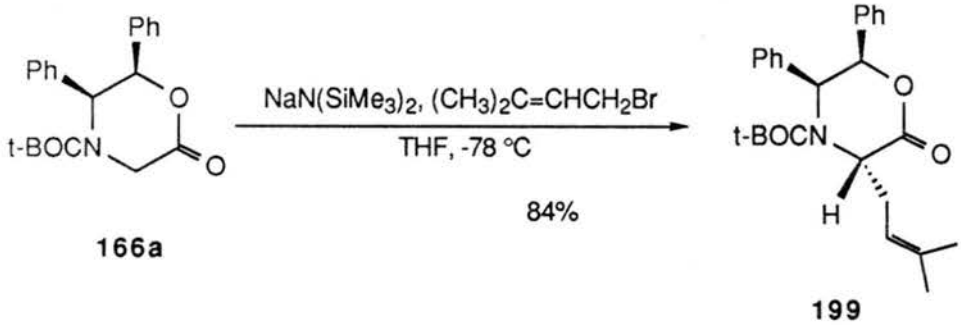


166a **207**

SCHEME 54



166a **190**

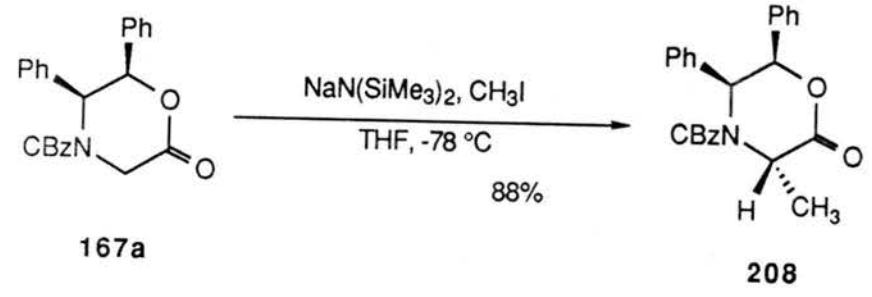


166a **199**

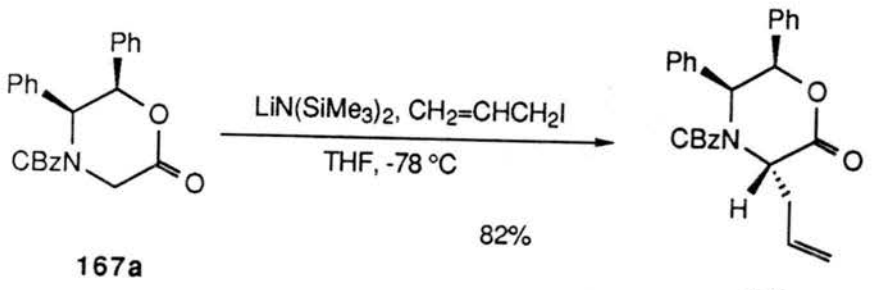
We also inspected the enolate alkylation with activated alkyl halides by employing the concomitant base/electrophile protocol. As shown in Scheme 54, the enolate alkylation with allyl iodide and dimethallyl bromide provided the homologated lactones **190** and **199**, respectively, in much better yields than that achievable by the previous method.

The CBz protected methyl and allyl lactones **208/209** were also prepared in excellent yields by treatment with the corresponding alkyl halides (Scheme 55).

SCHEME 55

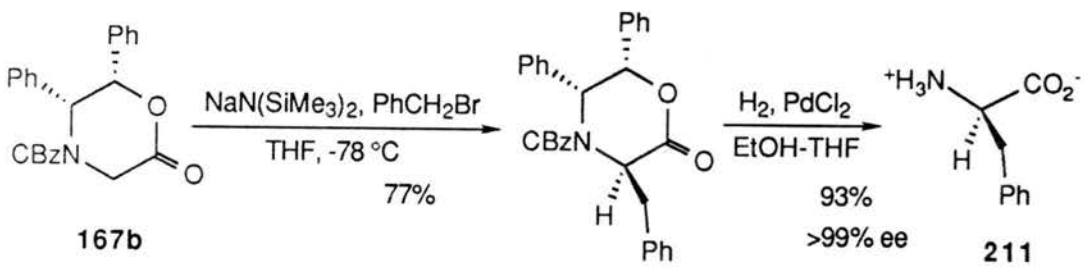


167a **208**



167a **209**

SCHEME 56



167b **210** **211**

As shown in Scheme 56, the benzylated oxazinone **210** was obtained in good yield by the reaction of the oxazinone **167b** with benzyl bromide in the presence of sodium bis(trimethylsilyl)amide and directly converted into the unnatural (D)-(2R) phenylalanine (**211**).

The enantiomeric excess of each amino acid was determined by acylation of the corresponding ethyl or methyl ester with either (+)- or (-)-α-methoxy-α-trifluoromethyl phenyl acetyl chloride 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 enantiomeric excess was observed.

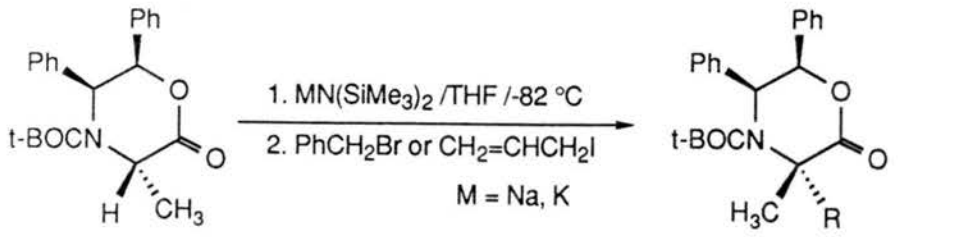
As discussed above, the new concomitant protocol can give rise to a wide variety of α-amino acids. With these encouraging results we examined the double alkylation of the oxazinones to obtain α-disubstituted amino acids which have recently attracted a great deal of interest from organic chemists. The results are discussed in the following paragraphs.

B. Synthesis of α-Disubstituted Amino Acids

α-Disubstituted amino acids have been attracting medicinal and biochemical interests being powerful enzyme inhibitors for e.g., dopa,[60] ornithine,[61] glutamate,[61] S-adenosylmethionine (SAM) decarboxylases,[62] and aspartate aminotransferase.[63] They have also found utility as conformational modifiers for physiologically active peptides.[64]

We first examined the enolate alkylation of α-methyl substituted oxazinone **192** by employing the standard method described in Part A. As shown in Scheme 57 the sodium enolate had been generated in THF for 35 min at -82°C and then quenched with benzyl bromide. Unfortunately the homologated product **212** was not detected. The experiment using potassium bis(trimethylsilyl) amide and allyl iodide gave a similar result with no

SCHEME 57

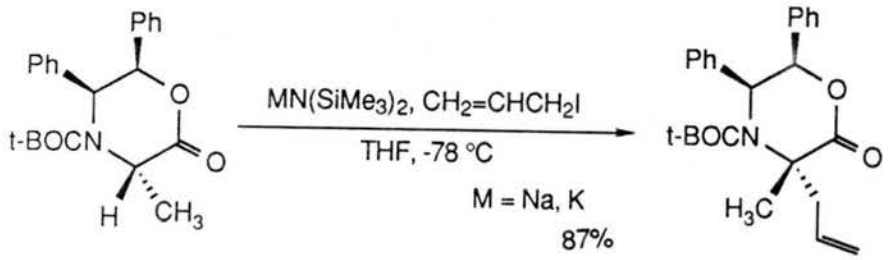


192

212 R : CH_2Ph

213 R : $CH_2=CHCH_2$

SCHEME 58



192 **213**

detectable desired product **213**; only decomposition of the starting material was observed. Fortunately, it was found that the use of the chelating reagent DME (dimethoxyethane) as cosolvent gave a good result; the homologated oxazinone **212** and **213** were obtained in 40% and 90% yields, respectively. Further enolate alkylations using DME were not investigated due to the development of an alternative procedure that was found to be effective for monoalkylation of the oxazinones **166/167** with a wide variety of alkyl halides.

By employing the new protocol described in the previous section, the enolate alkylation of α-methyl substituted oxazinone **192** was realized as shown in Scheme 58. First, sodium bis(trimethylsilyl)amide was examined to

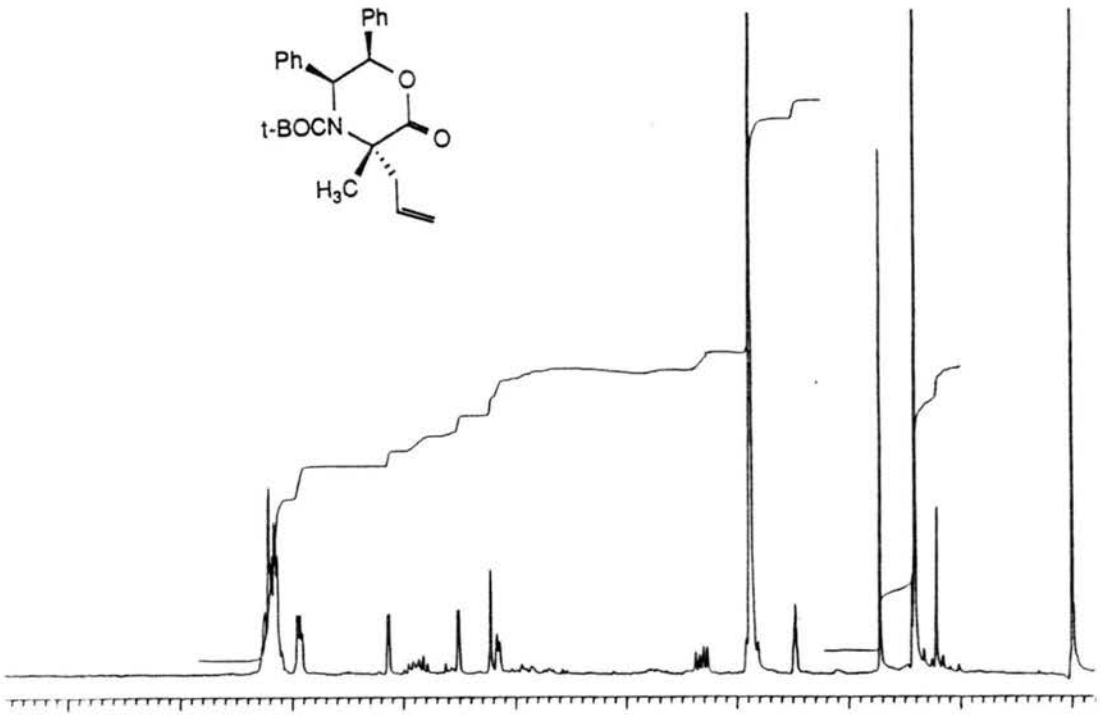
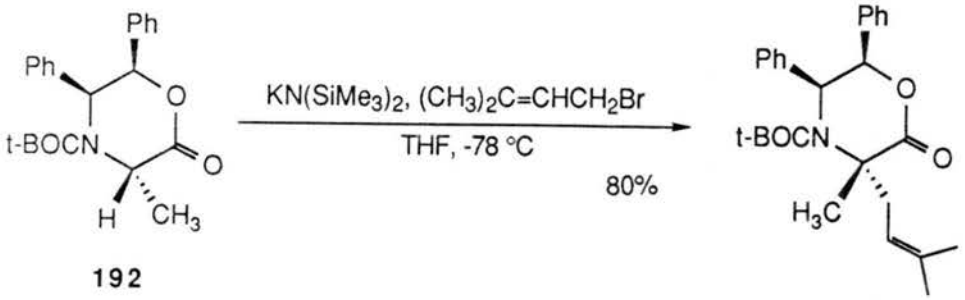


FIGURE 3 ^{1}H NMR of **213** in DMSO-d_6 at 393 °K

determine whether it is reactive enough for the double alkylation. To a solution of **192** and allyl iodide in THF-HMPA was added sodium bis(trimethylsilyl)amide at -78°C. The homologated oxazinone **213** was detected only in trace amounts by TLC. The same procedure was performed by using potassium bis(trimethylsilyl)amide instead of sodium bis(trimethylsilyl)amide. After standard aqueous work-up, the α-methyl-α-allyl oxazinone **213** was produced in 57% yield. This substance proved to be one diastereomer by ^{1}H NMR analysis as shown in Figure 3. If the chelating reagent HMPA is not used as cosolvent, the yield is significantly enhanced (57% → 87%). It is presumed that the employment of HMPA is not effective for the more reactive potassium enolates and only promotes decomposition.

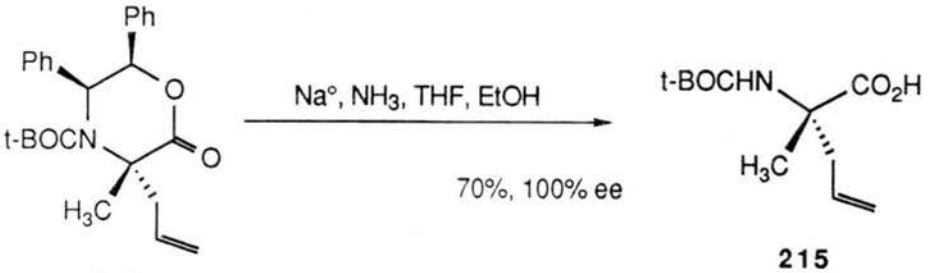
With this encouraging result, we studied another dialkylation. As shown in Scheme 59, the oxazinone **192** smoothly underwent coupling with dimethallyl bromide in the presence of potassium bis(trimethylsilyl)amide to afford the α-

SCHEME 59

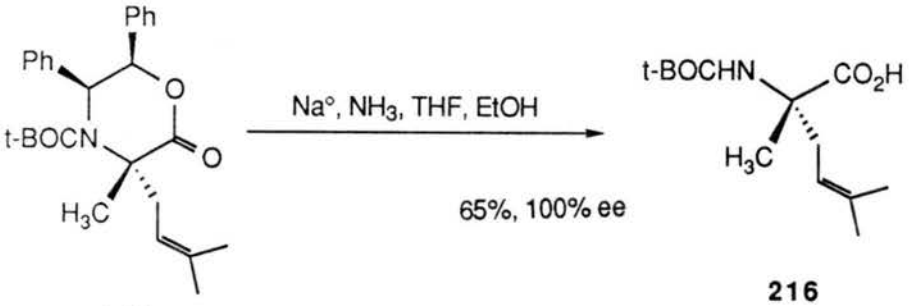


192 **214**

SCHEME 60



213 **215**

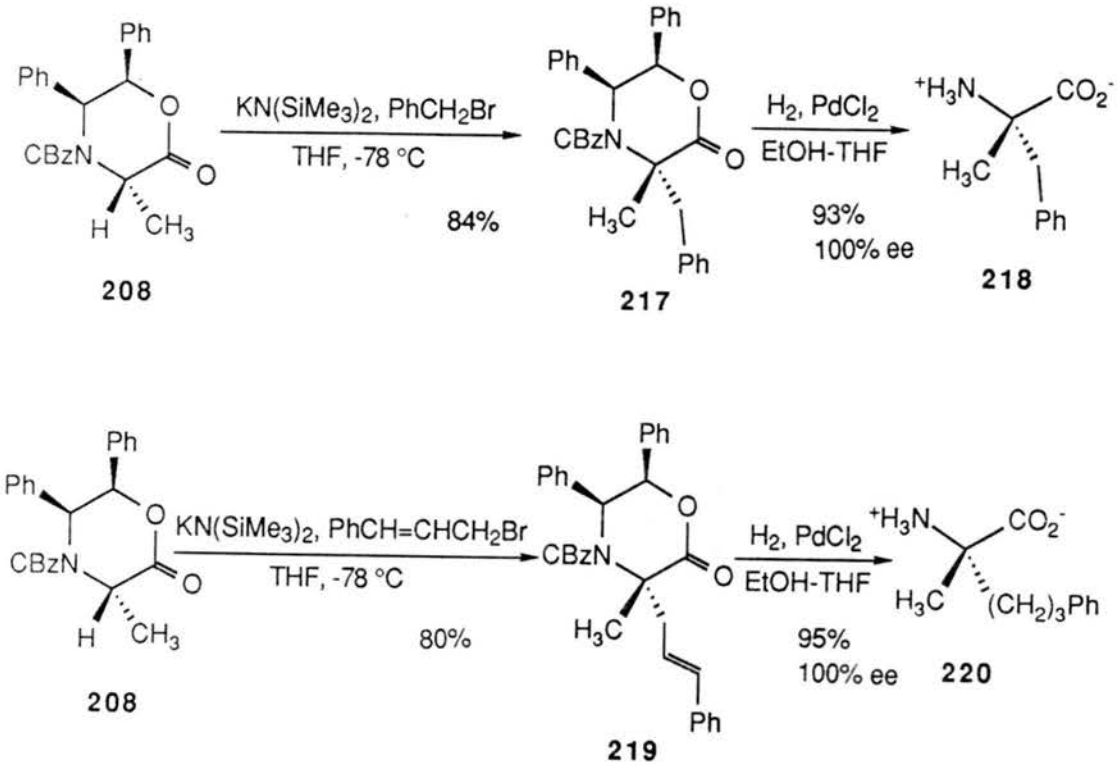


214 **216**

methyl-α-dimethallyl oxazinone **214** in 80% yield. As shown in Figure 4, high temperature ^{1}H NMR revealed that **214** was produced as a single diastereomer.

The disubstituted lactones **213** and **214** were smoothly converted into the N-t-BOC protected amino acids in good yields in the same manner (Na°/liquid ammonia) as the monosubstituted lactones. As shown in Scheme 60, addition of a THF solution of the oxazinone **213** and EtOH to a solution of

SCHEME 61



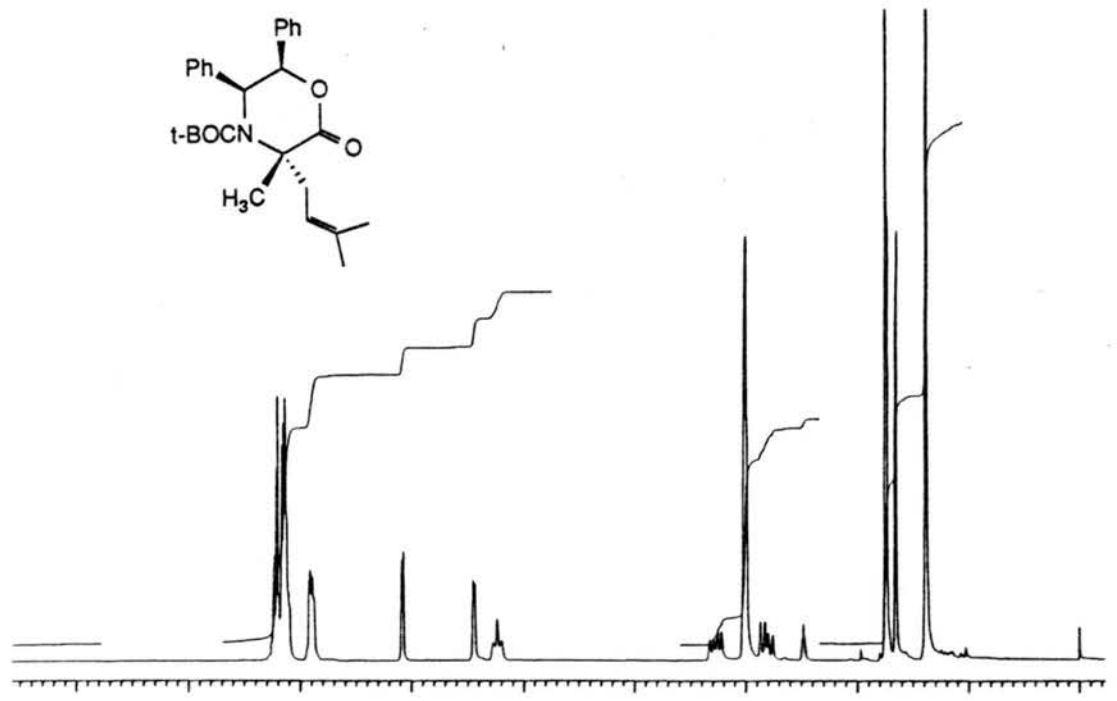


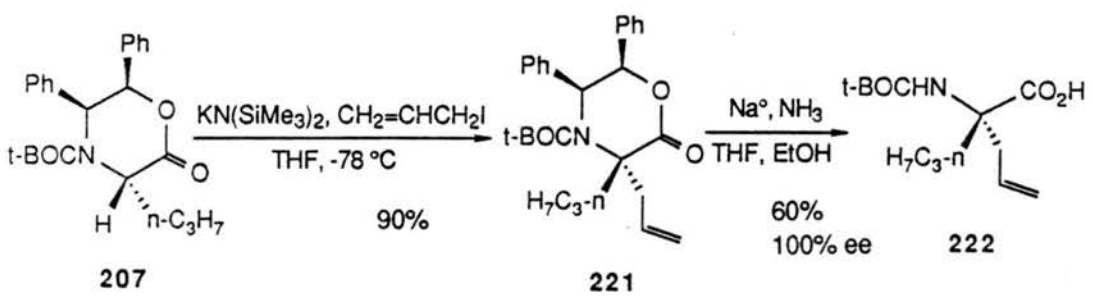
FIGURE 4 ^{1}H NMR of **214** in DMSO-d_6 at 393 °K

excess lithium metal dissolved in liquid ammonia smoothly led to the formation of the N-(*tert*-butyloxycarbonyl)alanine derivative **215** in high enantiomeric purity (~100% ee). The N-t-BOC-α-dimethallyl glycine **216** was also obtained by the same procedure (dissolving metal reduction of **214**) as one pure isomer in ~100% enantiomeric excess.

The dialkylation was also carried out on the CBz-protected methyl oxazinone **208**. As shown in Scheme 61, the enolate alkylation of **208** with benzyl bromide in the presence of potassium bis(trimethylsilyl)amide proceeded smoothly to afford the homologated lactone **217** in 84% yield. Similarly, treatment of **208** with cinnamyl bromide provided the disubstituted lactone **219** in 80% yield. The homologated oxazinones **217** and **219** were directly converted into the corresponding zwitterionic amino acids **218** and **220**, respectively, using the same method as that employed for the monoalkylated oxazinones. Again, high chemical yields and high optical purities were obtained (100% ee's).

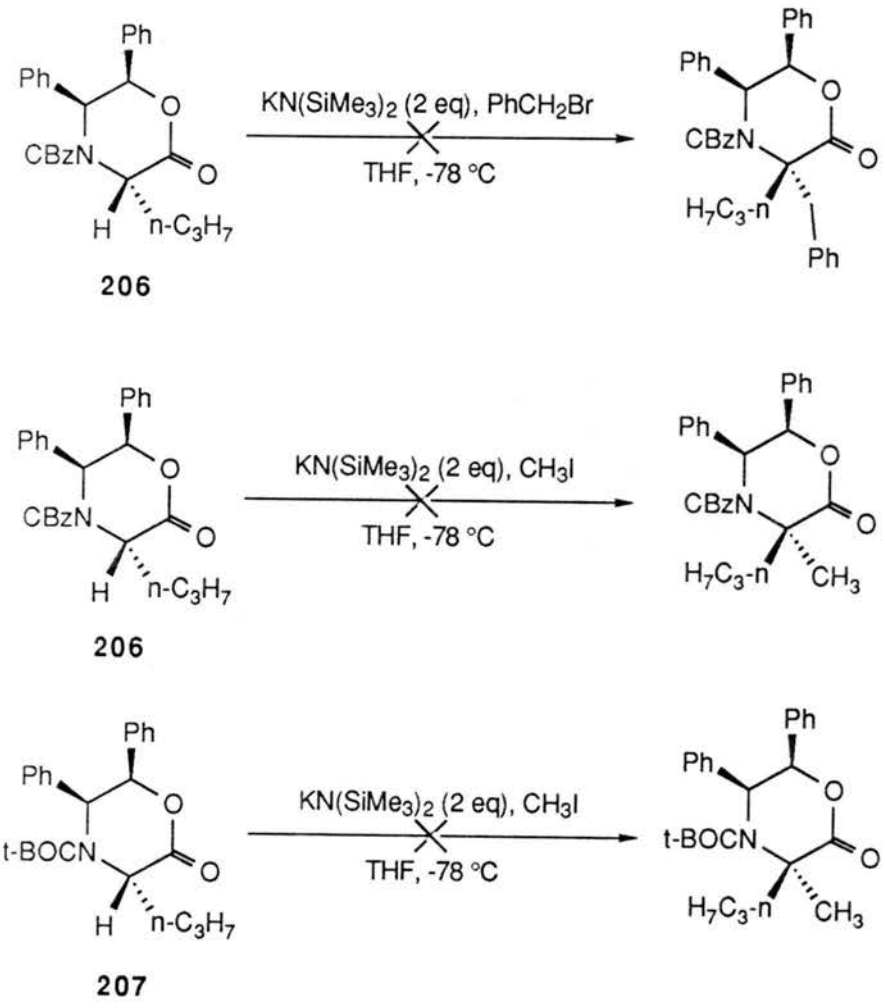
Next, we decided to study the enolate alkylation of more congested oxazinones which were expected to be more difficult to obtain. As shown in Scheme 62, the n-propyl oxazinone **207** underwent coupling with allyl iodide in the presence of potassium bis(trimethylsilyl)amide to afford the allyl n-propyl

SCHEME 62



207 **221** **222**

SCHEME 63



oxazinone **221** in 90% yield. The homologated lactone **221** was directly converted into the N-t-BOC amino acid **222** by dissolving metal reduction. Again, an essentially optically pure amino acid was obtained (100% ee).

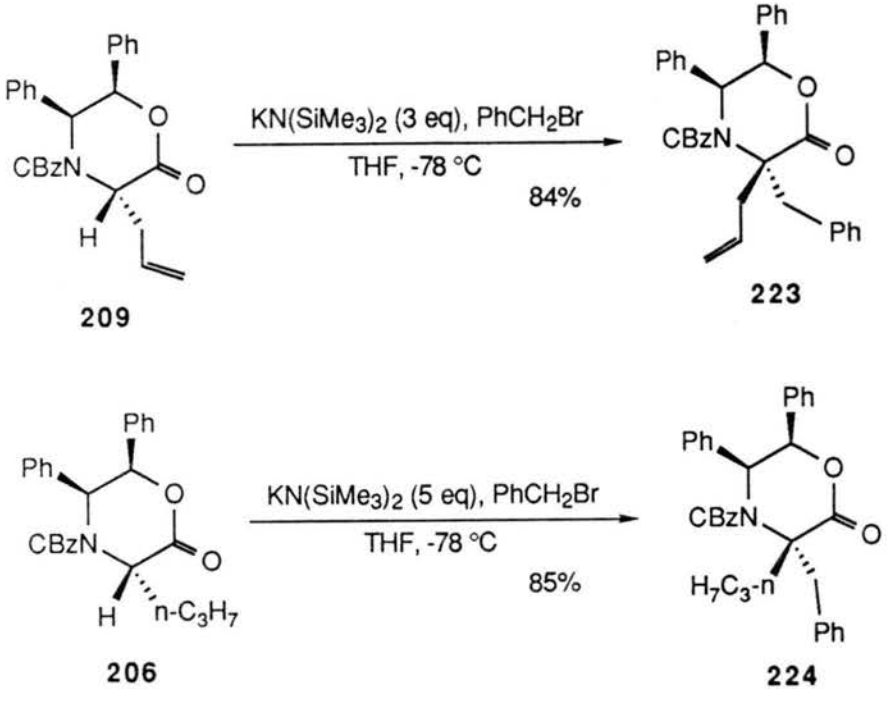
The dialkylation of the oxazinone **206** or **207** with less reactive alkyl halides relative to allyl iodide was studied by employing the same protocol described above; addition of potassium bis(trimethylsilyl)amide to a THF solution of the oxazinone **206/207** and benzyl bromide or methyl iodide at -78°C, then quenching with H_2O after 30-40 min. Unfortunately, treatment

of **206** or **207** with benzyl bromide or methyl iodide did not furnish the desired products (Scheme 63).

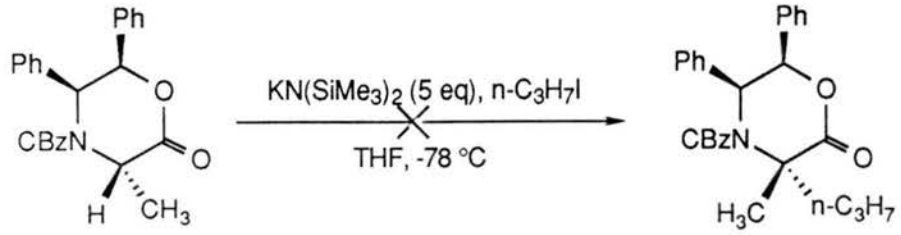
In all of the cases presented above, the enolate alkylations were performed by using 2 equivalents of potassium bis(trimethylsilyl)amide. We were surprised to find that the employment of excess base for the dialkylation of hindered oxazinones solved this problem. As shown in Scheme 64, the allyl lactone **209** was alkylated efficiently with benzyl bromide in the presence of 3 equivalents of potassium bis(trimethylsilyl)amide to furnish the allyl benzyl oxazinone **223** in 84% yield. The enolate alkylation of **206** required 5 equivalents of potassium bis(trimethylsilyl)amide.

The dialkylation with unactivated alkyl halide was also investigated. As shown in Scheme 65, the homologation of **208** was not successful, giving exclusively decomposition.

SCHEME 64

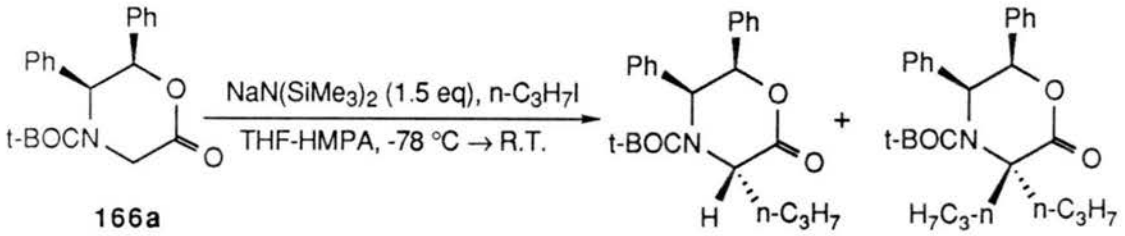


SCHEME 65



208

SCHEME 66



166a **207** **225**

In most of the monoalkylations studied, the dialkylated product is also obtained. Even in the case of the n-propyl lactone **207** (Scheme 66), the congested n-propyl oxazinone **207** underwent the coupling reaction with unactivated n-propyl iodide in the presence of a mere 1.5 equivalents of sodium bis(trimethylsilyl)amide. These results are still quite puzzling.

The enantiomeric excess of each amino acid was determined using the same protocol as that employed for the monosubstituted amino acids. Formation of the methyl esters of the dialkylated amino acids did not take place in refluxing 1N methanolic hydrochloride solution. The employment of more drastic conditions (~5N HCl-MeOH/refluxing) led to complex reaction mixtures. A method to prepare the methyl esters of the hindered dialkylated amino acids is described in detail in experimental section. Table 5 summarizes the results discussed above; dialkylation yield, amino acid yield and % ee.

TABLE 5

Entry	Oxazinone Substrate	Yield	RX	Base (Equivalent)	Amino Acid Yield	%ee
1	**192**	trace	CH_2=$CHCH_2I$	$NaN(SiMe_3)_2$	(2)	
2	**192**	57	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$	(2)	
3	**192**	87	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$	(2) 70	100
4	**192**	80	Me_2C=$CHCH_2Br$	$KN(SiMe_3)_2$	(2) 65	100
5	**207**	90	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$	(2) 60	100
6	**208**	84	$PhCH_2Br$	$KN(SiMe_3)_2$	(2) 93	100
7	**208**	80	PhCH=$CHCH_2Br$	$KN(SiMe_3)_2$	(2) 95	100
8	**206**	0	$PhCH_2Br$	$KN(SiMe_3)_2$	(2)	
9	**206**	38	$PhCH_2Br$	$KN(SiMe_3)_2$	(4)	
10	**206**	85	$PhCH_2Br$	$KN(SiMe_3)_2$	(5)	
11	**209**	84	$PhCH_2Br$	$KN(SiMe_3)_2$	(3)	

Entries 1-2; HMPA-THF (10:1) was used as solvent.
Entries 3-11; THF was used as solvent.

As expected, the second alkylation proceeded *anti-* to the two phenyl rings of the oxazinone. A single crystal X-ray analysis of **217** further corroborates this as shown in Figure 5. The structure clearly shows that the attack of the electrophile to the enolate occurs from the less hindered face of the oxazinone enolate.

This protocol is quite useful for the preparation of a wide variety of α-disubstituted amino acids with predetermined stereochemistry by employing each enantiomorphic form of the oxazinone. On the other hand, most other methods (particularly Schöllkopf and Seebach's) have a preassigned substituent derived from the precursor amino acid within the template and

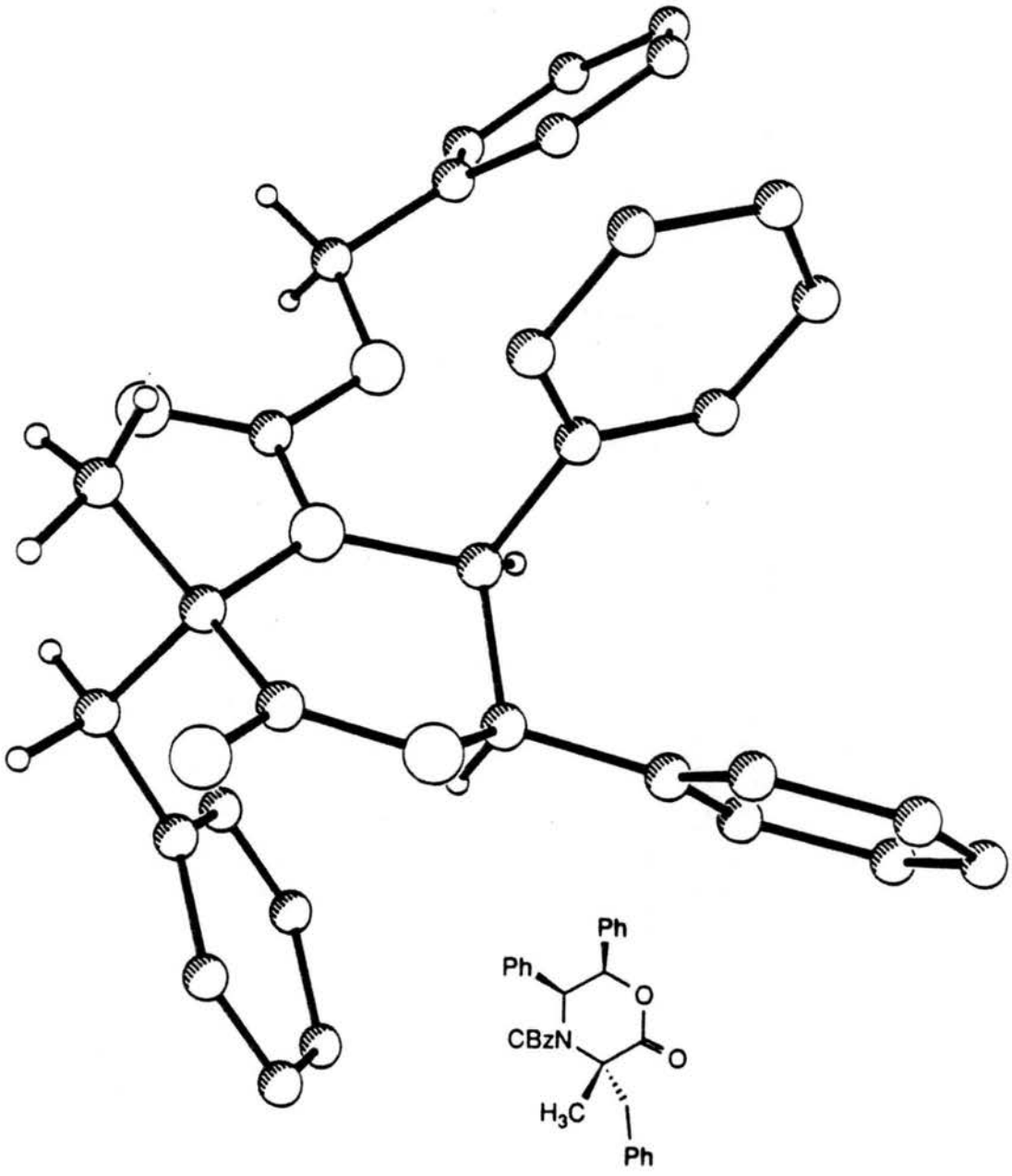
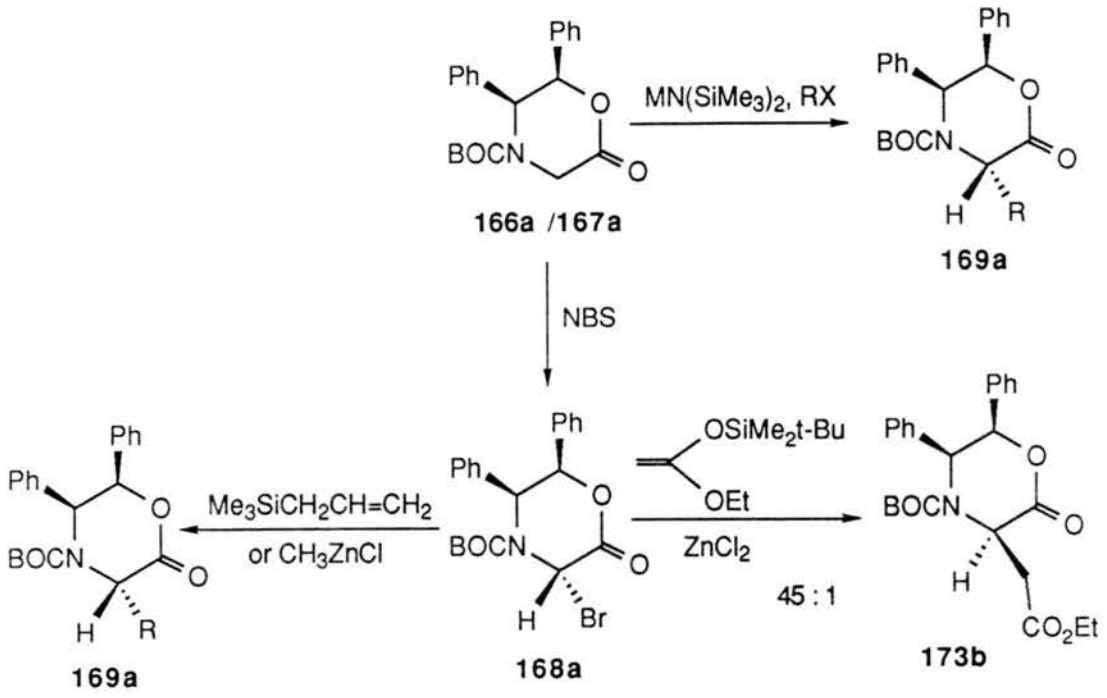


FIGURE 5 Molecular Structure of **217**. Atoms are shown as spheres of fixed, arbitrary radius.

therefore require preparation of each template for each synthetic application. In the present case, final deblocking to the amino acids is readily performed under mild reductive conditions in the same way as described for the α-monosubstituted amino acids while, in most other syntheses, hydrolysis for the final deprotection requires drastic conditions or even fails. The direct method to prepare N-t-BOC protected disubstituted amino acids, which are in suitable forms for direct peptide coupling, is very advantageous because acylating dialkylated amino acids is not readily achieved as will be discussed in Chapter 4.

It is worthwhile to compare the complementary cationic and anionic reactivities of the oxazinones for constructing variously substituted α-amino acids. As shown in Scheme 67, the amino acids alanine and allyl glycine have been prepared from the electrophilic route by use of CH_3ZnCl and allyltrimethylsilane couplings, respectively. In both cases, the *anti-* oxazinones are obtained. The alkylation of the enolate derived from **167a** by CH_3I and allyl iodide led to the same relative stereochemistry. However, the yield of the CH_3I alkylation (88%) is far superior to the CH_3ZnCl coupling to the α-bromolactone (46%) due to a competing 1-electron reduction pathway observed for these relatively basic organometallic reagents. In the allyl case, alkylation of the enolate derived from the lactone **166a** with allyl iodide also gave a higher yield (86%) than the allyltrimethylsilane coupling to the electrophilic system (63%). The ethyl bromoacetate alkylation also furnishes the *anti-* oxazinone as the exclusive product. The *syn-* oxazinone, however, is obtained in similar yield and % ee by coupling the ketene silyl acetal of ethyl acetate to the electrophilic system **168a**. A 45:1 ratio of *syn:anti* products results from S_N2' displacement of the *anti*-α-bromide **168a** derived from **167a** in this coupling. The phenylalanine manifold, which is not readily

SCHEME 67



accessible from the electrophilic system, can be readily prepared by alkylation of the enolate with the appropriate benzylic halide. The coupling *via* the enolate derived from the α-monosubstituted lactones also provides access to a wide variety of α-disubstituted amino acids which cannot be prepared by the electrophilic route.

The commercially available oxazinones **166/167** can serve as useful templates for the preparation of various α-monosubstituted and α-disubstituted amino acids. Although the chiral auxiliary is sacrificed in the final reductions, this system offers an important advantage over numerous other amino acid syntheses that require expensive, time-consuming chromatographic separation, recovery and 'recycling' of chiral auxiliaries (rarely done in practice) and hydrolysis of esters, etc. to obtain the free zwitterionic amino acids. In the present case the chiral auxiliaries are polar, water-soluble substances that, even if it were possible to recover, would require a difficult

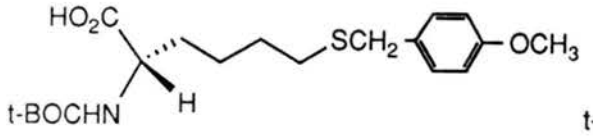
separation from the products. Thus, the destruction of the chiral auxiliary in this case turns out to be a significant *advantage* since the final processing converts the chiral auxiliary into an innocuous substance (bibenzyl) of greatly different solubility properties than the amino acids or t-BOC amino acids and is easily removed by trituration or extraction with a non-polar solvent.

The enolate approach discussed herein, provides diverse α-monosubstituted amino acids through nucleophilic carbanion alkylation in high optical purity (95.9-100% ee's). This approach also provides access to α-disubstituted amino acids in essentially optically pure forms (100% ee's). The present technology nicely complements the electrophilic couplings and can be applied to the synthesis of complicated amino acids. The following two chapters will include the preparation of complex amino acids by employing this enolate alkylation strategy.

CHAPTER 3

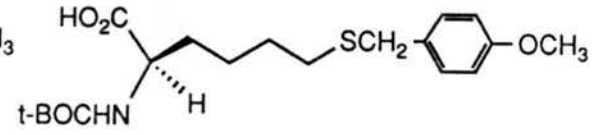
SYNTHESIS OF (D)- AND (L)-2-(t-BUTYLOXYCARBONYL)AMINO-6-(*p*-METHOXYBENZYL)THIONOHEXANOIC ACID

We decided to synthesize 2-(t-butyloxycarbonyl)amino-6-(*p*-methoxybenzyl)thionohexanoic acid **226** in both enantiomeric forms. This protected "extended cysteine" residue was to be examined for preparing stabilized helix-turn-helix peptides; a common motif in DNA-binding proteins.



L - ISOMER

226a

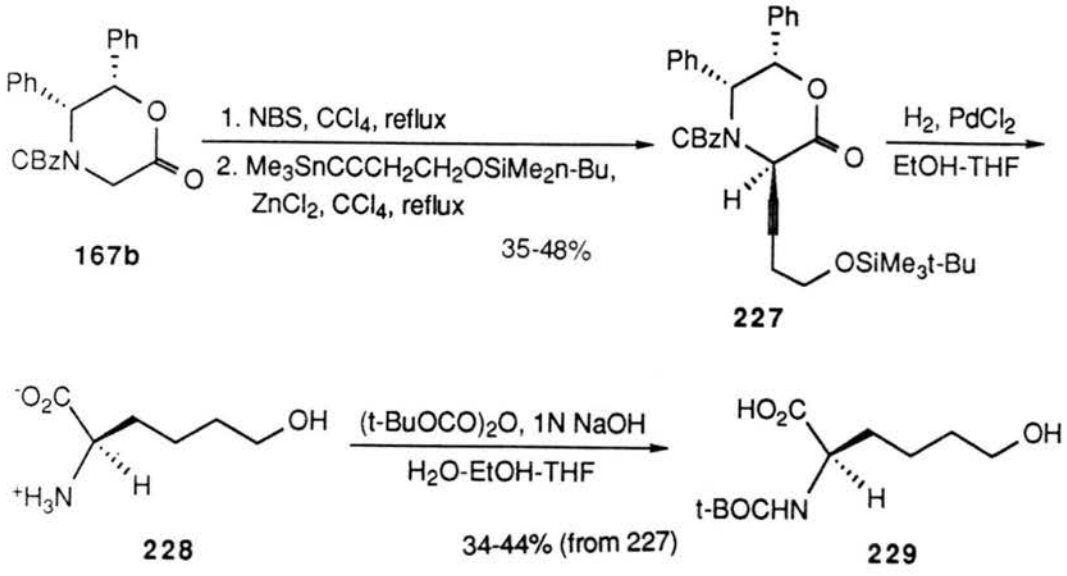


D - ISOMER

226b

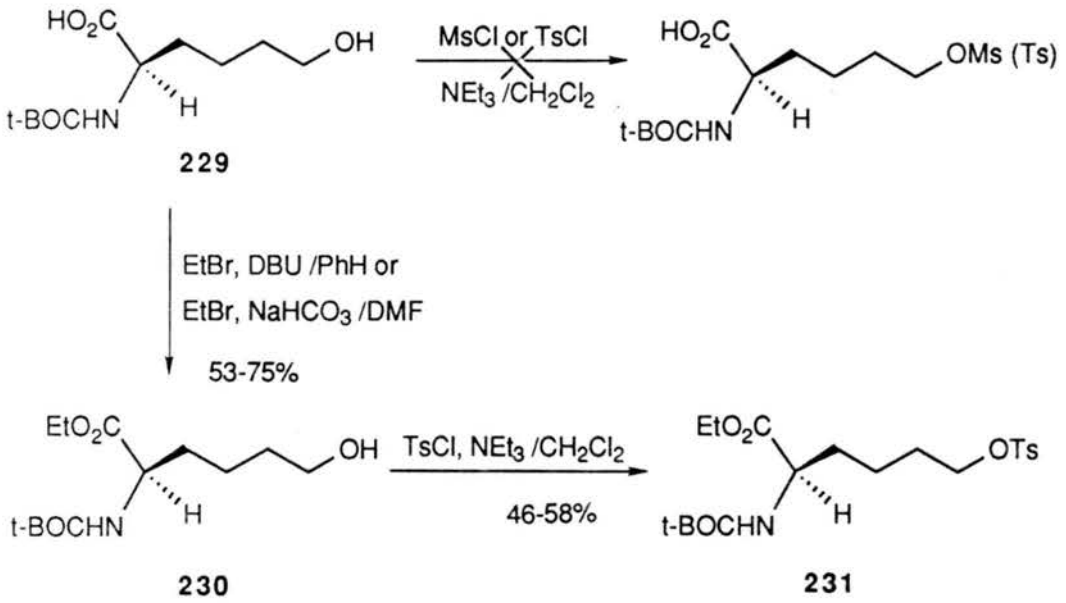
First, we attempted to prepare the D-isomer by coupling the (4'-t-butyldimethylsiloxy)butynyltrimethyl tin to the electrophilic bromooxazinone **168b** using the method developed by Williams and Zhai[54] as introduced in Chapter 1. As shown in Scheme 68, the oxazinone **167b** is brominated and then condensed with trimethyl tin acetylide in the presence of zinc chloride in refluxing carbon tetrachloride to afford the crystalline *anti*- alkyne **227** as a single diastereomer in 35-48% yield. Catalytic hydrogenation of **227** in the presence of palladium chloride in the usual way gave rise to a complex reaction mixture. The desilylated amino acid **228** was obtained as the major product but proved difficult to purify. The crude amino acid **228** was acylated

SCHEME 68

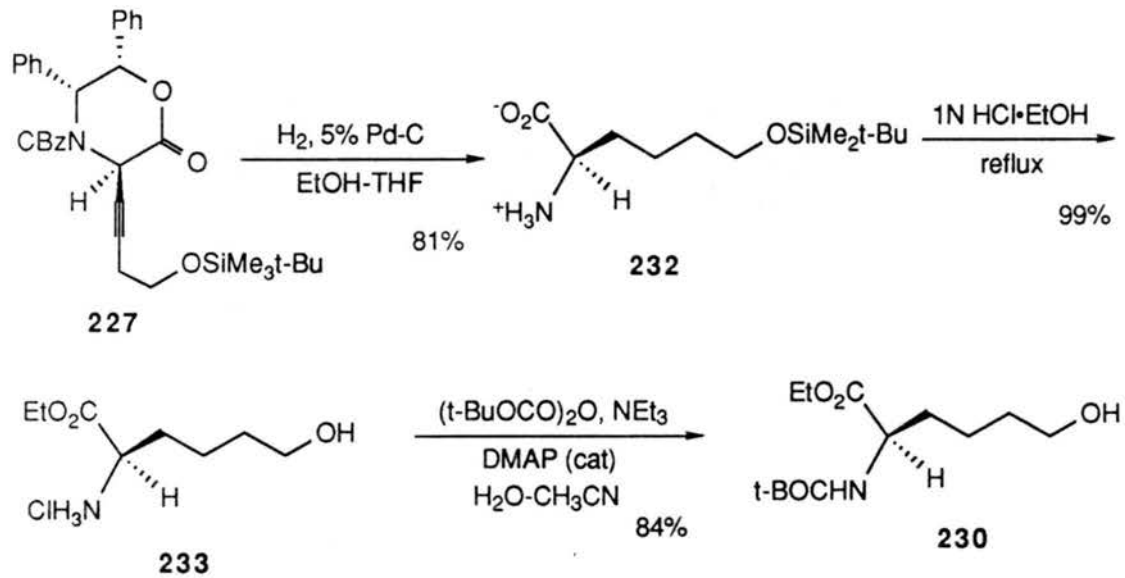


without purification to afford the N-t-BOC amino acid **229** in 34-44% yield (from **227**). In an effort to introduce the sulfhydryl residue, the sulfonylation of **229** was examined. As shown in Scheme 69, the attempted mesylation or tosylation of **229** proved to be unsuccessful. Compound **229** was esterified to afford the hydroxy ester **230** (53-75% yield) which was successfully converted into the tosylate **231**. At this point, we discovered a more efficient route to prepare the hydroxy ester **230**. As shown in Scheme 70, the catalytic hydrogenation of **227** over 5% Pd/C at atmospheric pressure gave rise to a clean reduction to afford the zwitterionic amino acid **232** which was directly converted into the amino acid ester hydrochloride salt **233** in refluxing ethanolic HCl solution. It is quite curious that 5% Pd-C cleanly effected the hydrogenation of **227** since attempted deblocking of other homologated oxazinones with 5% Pd/C had never proved to be successful. Acylation of **233** with $(BOC)_2O$ in the presence of DMAP as a catalyst and triethyl amine afforded the N-t-BOC amino acid **230** in high yield (84%).

SCHEME 69

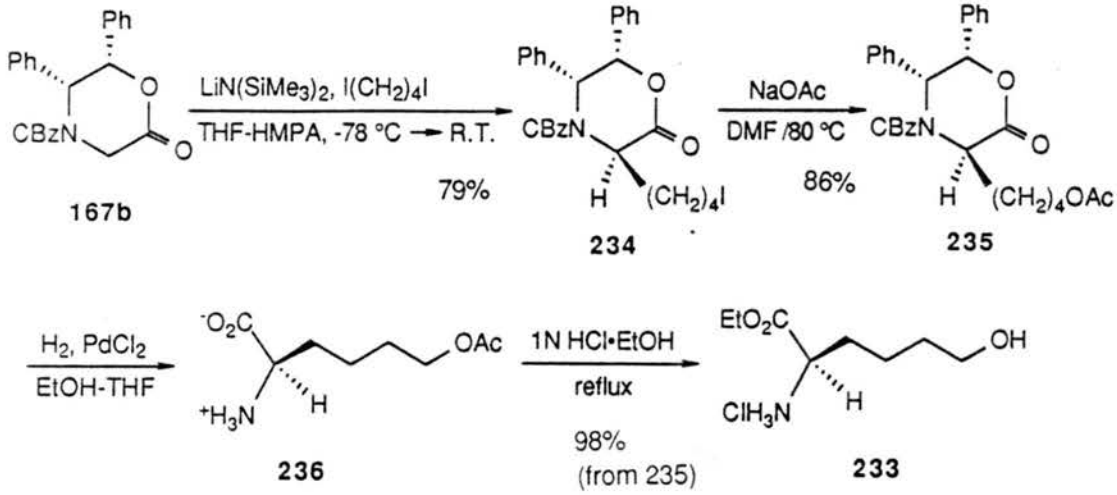


SCHEME 70

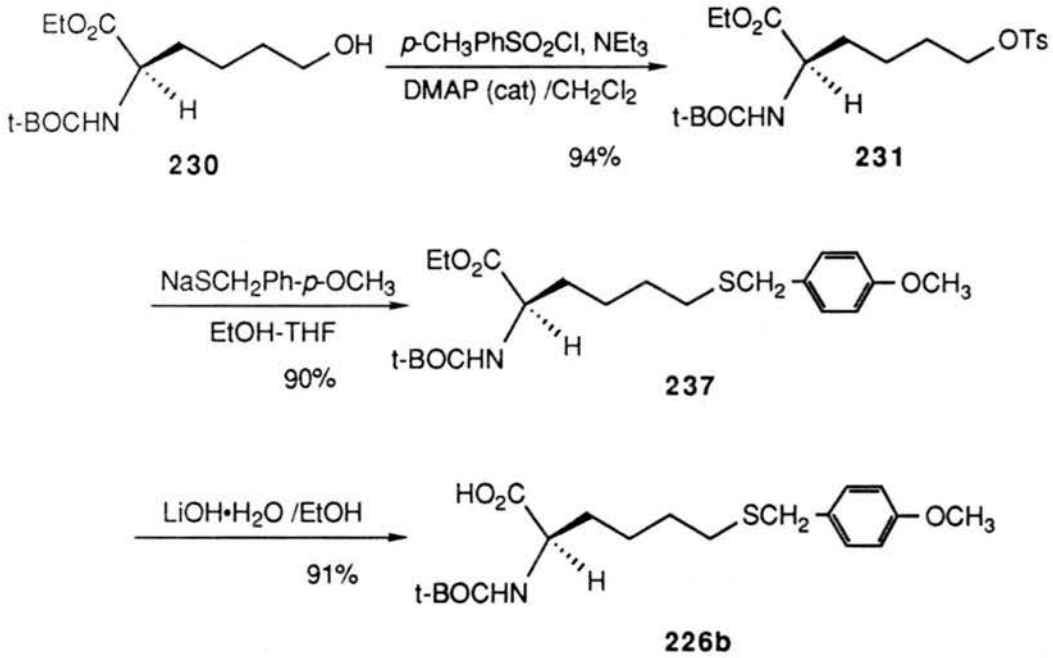


The synthesis of **230** remains problematic because separation of the alkyne **227** from the reaction mixture is difficult and the yield is low (35-48%). In an effort to overcome these problems, the enolate coupling of **167b** was studied. As shown in Scheme 71, generation of the enolate from **167b** and subsequent treatment with 1,4-diiodobutane in the presence of lithium

SCHEME 71



SCHEME 72



bis(trimethylsilyl)amide furnished the homologated iodide **234** in 79% yield. The displacement of iodide by acetate in hot DMF afforded the acetate **235** in 86% yield. Catalytic hydrogenation over $PdCl_2$ by the standard method gave the amino acid **236** which was converted into the amino ester salt **233** (98%, two steps) in refluxing ethanolic HCl solution. This method is advantageous in that: (1) the homologated lactone **234** does not require silica gel separation,

(2) crystalization in hexanes gives material of sufficient purity for the next reaction, and (3) a high yield is obtained.

As shown in Scheme 72, treatment of **230** with tosyl chloride in the presence of triethylamine and a catalytic amount of DMAP furnished the tosylate **231** in 94% yield. As presented in Scheme 69, the tosylation in the absence of acylating reagent DMAP gave the tosylate in only 46-58% yield accompanied by a substantial amount of unreacted starting material.

Nucleophilic substitution of the tosylate with *p*-methoxybenzyl thiol produced the sulfide **237** (90%). This compound proved to be very unstable to silica gel and air, and required immediate purification and careful handling. Finally, the ester was hydrolyzed in ethanolic lithium hydroxide solution to afford the D- amino acid **226b**. The enantiomer **226a** was prepared in the same manner as the D- isomer.

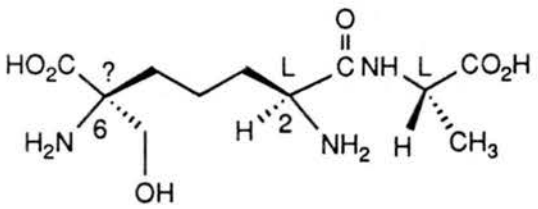
The enantiomeric excess of each isomer was determined using the intermediate acetate **236** because the ester of **226** was unstable and not isolable. In the case of the L- isomer, 97% ee was determined; the D- isomer was obtained in 100% ee.

The use of the protected "long cysteine" in peptide synthesis was examined in Professor Peter G. Schultz's laboratory at Berkeley. Compound **226b** was incorporated into several small peptides by standard carbodiimide coupling chemistry. Unfortunately, all attempts to cleave the *para*-methoxybenzyl group to release the free sulfhydryl (HF, DDQ, TFA, etc.) resulted in cleavage of the non-benzylic C-S bond.

CHAPTER 4

SYNTHETIC APPROACH TO N-(2,6-DIAMINO-6-HYDROXYMETHYLPIMELYL)-L-ALANINE

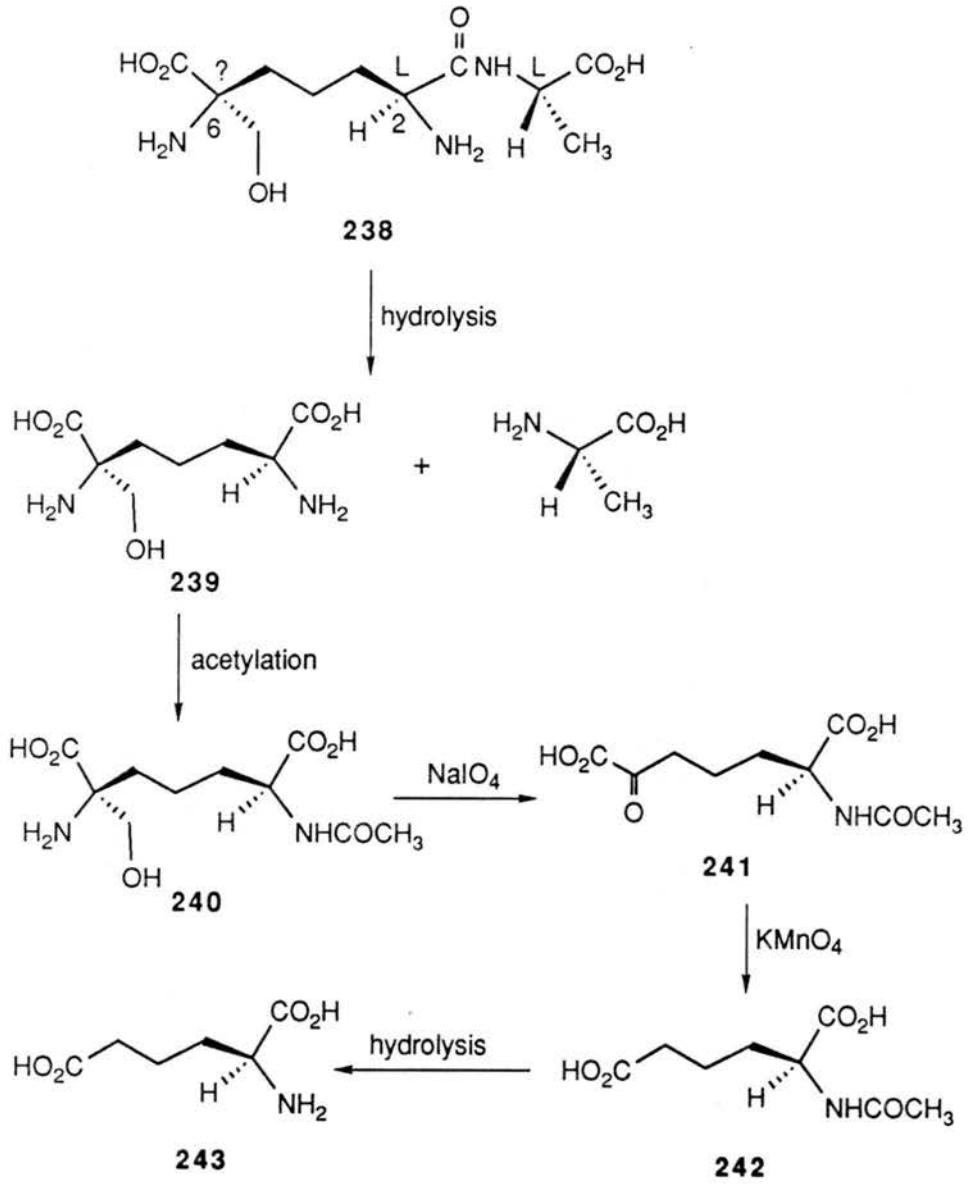
A novel dipeptide,[65] N-(2,6-diamino-6-hydroxymethylpimelyl)-L-alanine (**238**), was isolated from the culture broth of a microorganism identified as *Micromonospora chalcea* by Shionogi Co. in Japan.



238

The structure of this substance was determined by spectroscopic methods and chemical degradation. In detail, the following sequence was performed to identify the structure of this natural product. The natural substance was assumed to be a dipeptide composed of an unknown amino acid and alanine. This was established by hydrolysis and subsequent analysis of the hydrolyzate by an automatic amino acid analyzer. Specific optical rotation value and ORD spectrum proved that the alanine has the L-configuration. Elemental analysis indicated that the molecular formula of the unknown amino acid is $C_8H_{16}N_2O_5$. Furthermore, ^1H and ^{13}C NMR data suggested that the unknown amino acid should be 2,6-diamino-6-

SCHEME 73



hydroxymethylpimelic acid (**239**). To obtain further evidence of the suggested structure and stereochemistry of the unknown amino acid, chemical transformations were performed. As shown in Scheme 73, the amino acid **239** was acetylated with acetic anhydride in a dilute sodium bicarbonate solution and then treated with $NaIO_4$ in a dilute alkaline solution to afford **241**. Oxidation of **241** with $KMnO_4$ and subsequent hydrolysis furnished α-amino adipic acid (**243**). Comparison of **243** with an authentic

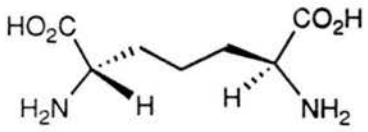
sample indicated that the α-aminoadipic acid has the L-configuration. Thus, the unknown amino acid proved to be 2,6-diamino-6-hydroxymethylpimelic acid with the L-configuration at the C_2-stereogenic center. However, the relative and absolute stereochemistry at C-6 are unknown. Finally, the dipeptide proved to be the structure shown in Scheme 73 by the Scheinblatt method[66] which determines the sequence of amino acid residues in di- and tri-peptides by ^1H NMR techniques.

The dipeptide **238** exhibits limited antimicrobial activity against *E. coli* on a synthetic medium and this activity is synergistically enhanced by several cell wall synthesis-inhibitors such as penicillin G, phosphonomycin, cycloserine, chloro-D-alanine, macarbomycin and cephaloridine.

In spite of its weak biological activity, we decided to synthesize this natural product in a stereochemically unambiguous manner. In this way, we hoped to be able to assign the stereochemistry at C-6 and develop methodology that would be applicable to the 2,6-diaminopimelic acid (DAP) family of amino acids.

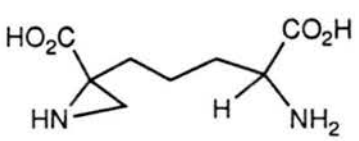
The L,L- and meso-DAP's (**244**) lie on the biosynthetic path to L-lysine in bacteria[67,68] as shown in Figure 6, and are key constituents of the peptidoglycan cell wall layer of most Gram-negative and some Gram-positive bacteria. Despite their importance, the asymmetric synthesis of DAP has not been reported yet.

Recent studies in several laboratories demonstrate that a number of compounds which inhibit the formation or metabolism of 2,6-diaminopimelic



L, L - DAP

244



245

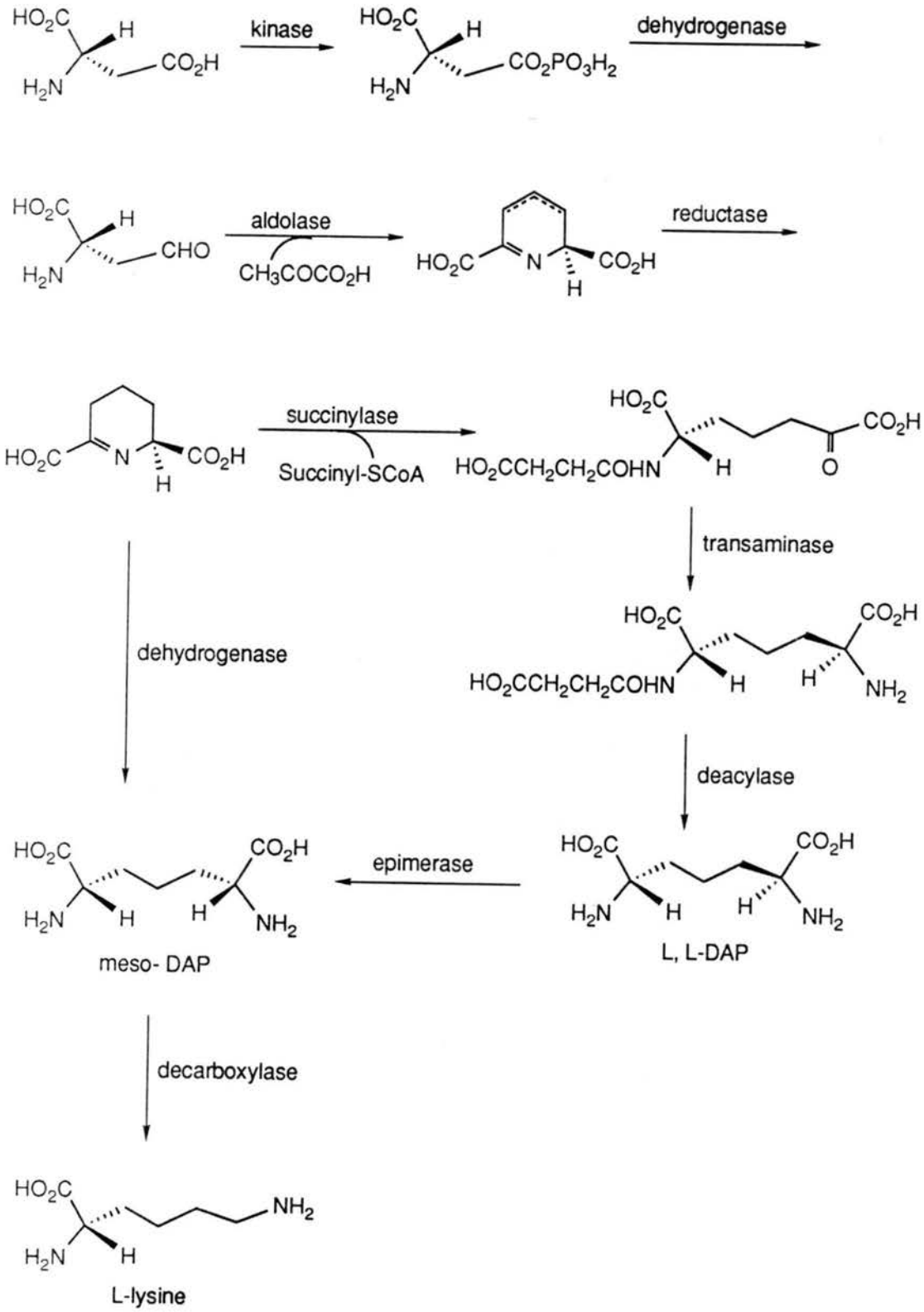


FIGURE 6 Biosynthetic pathway to diaminopimelic acid and lysine in bacteria

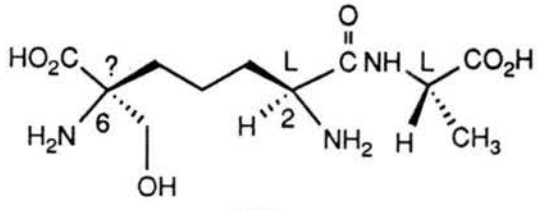
acid by bacteria possess antibiotic activity.[69,70] Since mammals lack the diaminopimelate pathway and require L-lysine in their diet,[71] specific inhibitors of the enzymes along this route are potential antimicrobial agents that should display low mammalian host toxicity.

2,6-Diamino-6-hydroxymethylpimelic acid is quite interesting in that it contains the basic DAP skeleton from which many DAP analogs might be prepared. These structural analogs might serve as substrates for the biosynthetic enzymes and, if incorporating appropriate functionality, might be capable of inhibiting these enzymes.

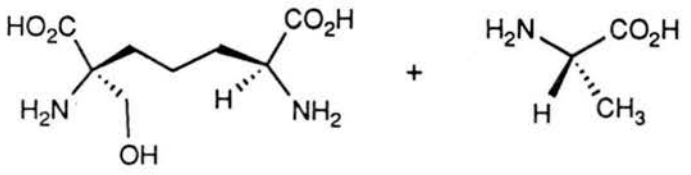
Recently it was reported[72] that 2-(4-amino-4-carboxybutyl)-aziridine-2-carboxylic acid (**245**, aziridino-DAP) is an extremely potent inhibitor of DAP-epimerase.

As shown in Scheme 74, the dipeptide could be synthesized by coupling 2,6-diamino-6-hydroxymethylpipemlic acid (**239**, HMDAP,

SCHEME 74



238

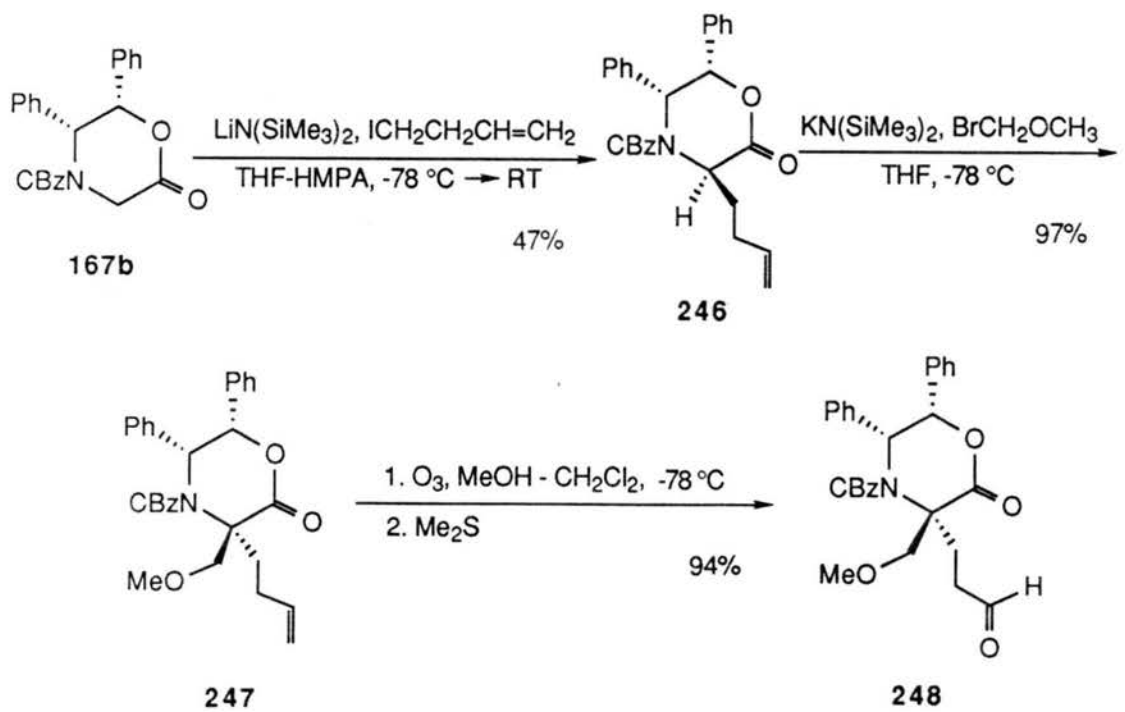


239 L- Alanine

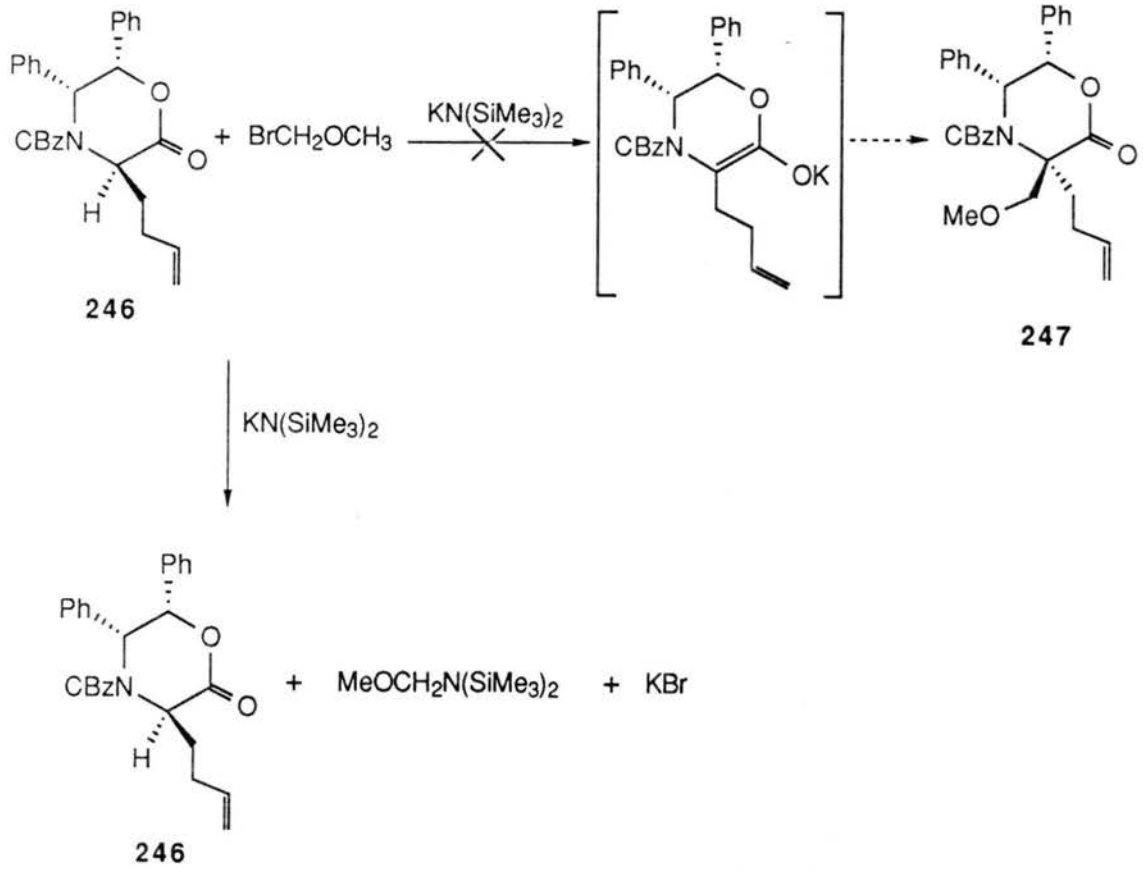
abbreviated from now on) and L-alanine. HMDAP was obtained by hydrolysis of the natural dipeptide.

First, we attempted to synthesize (2S,6R)-HMDAP. As shown in Scheme 75, the lactone **167b** was treated with homoallyl iodide in the presence of lithium bis(trimethylsilyl)amide to give the homoallyl oxazinone **246** in 47% yield. The dialkylation of **246** took place smoothly to furnish the methoxymethyl homoallyl oxazinone **247** in 97% yield. The standard protocol employing addition of potassium bis(trimethylsilyl)amide to a THF solution of the oxazinone and alkyl halide as described in Chapter 2 did not work in the present case giving only unreacted starting material. It is reasonable that the extremely electrophilic bromomethyl methyl ether consumes the base potassium bis(trimethylsilyl)amide as shown in Scheme 76. It was found that a slightly revised procedure gave satisfactory results. To a solution of **246** in

SCHEME 75



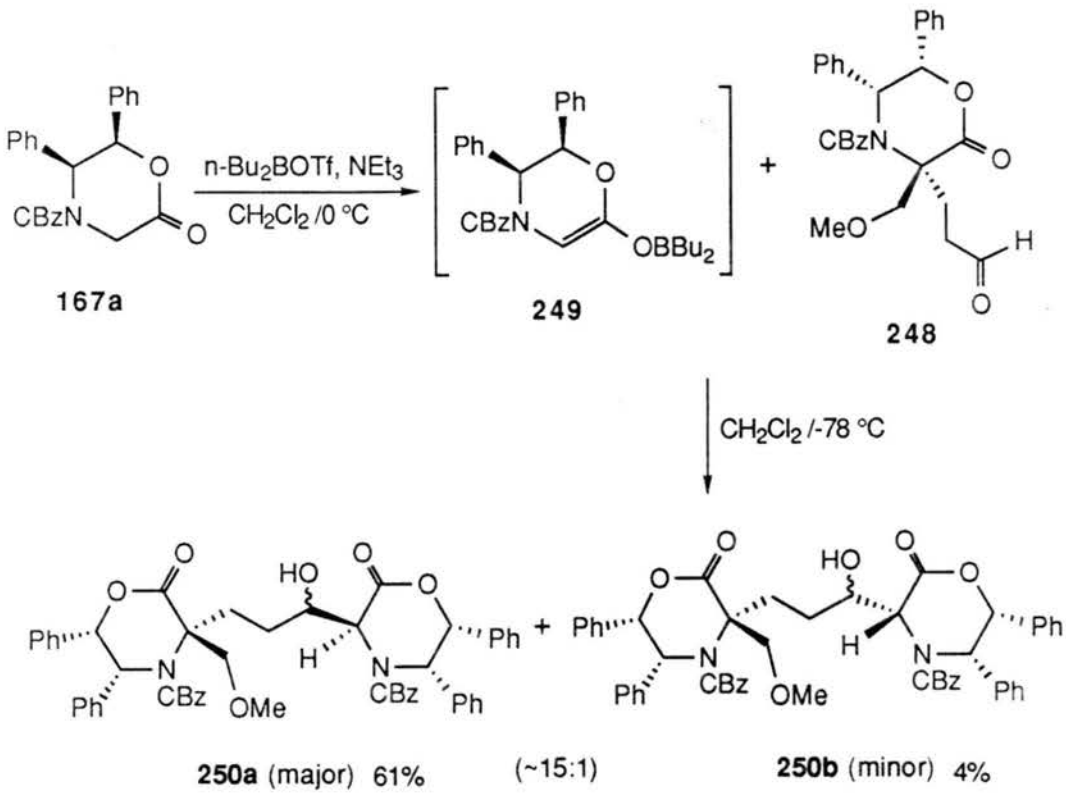
SCHEME 76



THF was added potassium bis(trimethylsilyl)amide. After 5 min, bromomethyl methyl ether was added. The homologated oxazinone **247** was ozonized and then quenched with dimethyl sulfide to afford the aldehyde **248** in 96% yield.

Next, we examined the coupling reaction of the aldehyde **248**. As shown in Scheme 77, the boron enolate of **167a** undergoes aldol condensation[73] with the aldehyde **248** to give the hydroxy dilactone **250a** (61%) as the major product and **250b** (4.1%) as the minor product. It is assumed that the relative stereochemistry of the minor diastereomer **250b** at the α-position is *syn*- to the two phenyl rings because the chemical shifts of methine protons at the benzylic positions are very different from those of major isomer **250a** by ^{1}H NMR analysis. As shown in Figure 7, for the *anti*-

SCHEME 77



diastereomer **250a**, the difference in chemical shift ($\Delta\delta$) for H_a and H_b is 1.26 ppm while $\Delta\delta$ for the *syn*- diastereomer is 0.47 ppm. This assignment is based on the assumption that both *syn*- and *anti*- diastereomers have similar chemical shifts for H_c and H_d; δH_c for *syn*- ~ δH_c for *anti*-, δH_d for *syn*- ~ δH_d for *anti*-. These relative chemical shift differences are in accord with empirical observations first discussed by Sinclair.[59]

It is quite interesting that empirical observations by Sinclair can be applied to the dialkylated lactone systems as will be described later on. As shown in Figures 8, 9 and 10, all the *anti*- diastereomers have larger $\Delta\delta$ values and all the *syn*- diastereomers have smaller $\Delta\delta$'s. The differences between two $\Delta\delta$'s for *anti*- and *syn*- isomers are much bigger (~0.8 ppm) than those of mono-alkylated lactone systems (~0.4 ppm); *syn*- 0.05, *anti*- 0.89 for **259**, *syn*- 0.45, *anti*- 1.21 for **265** and *syn*- 0.02, *anti*- 0.82 for **267**.

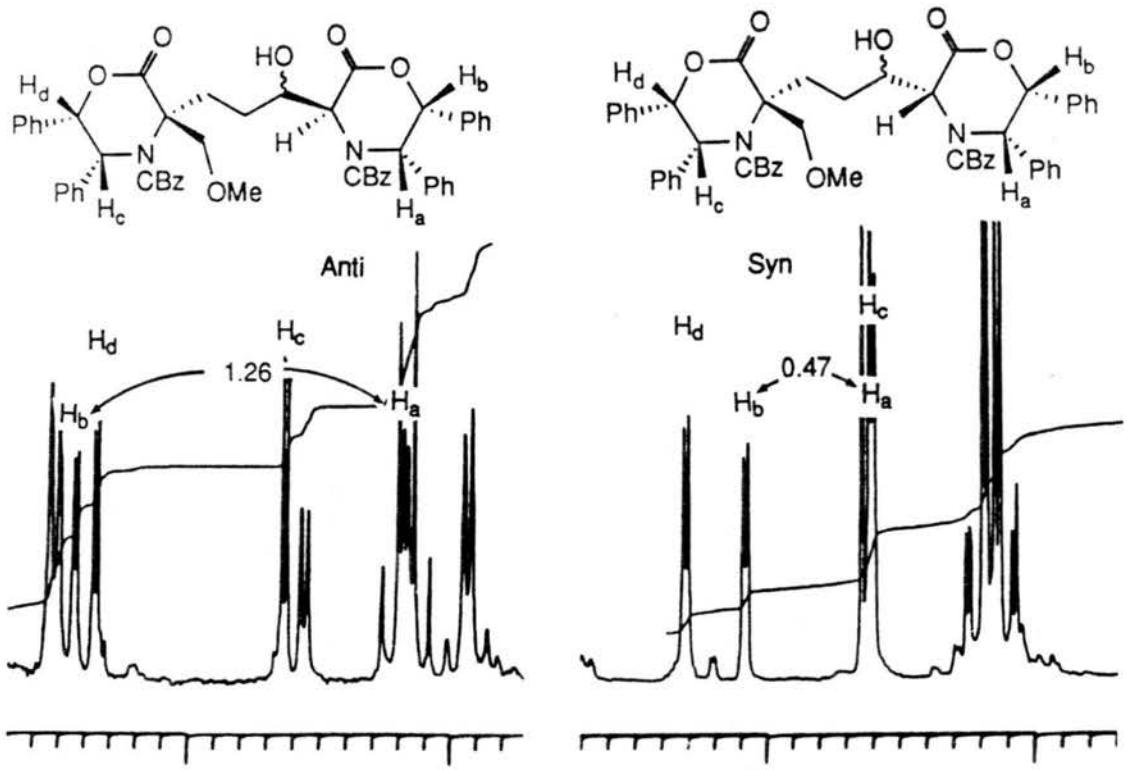


FIGURE 7 Relative $\Delta\delta$ of H_a and H_b for **250**

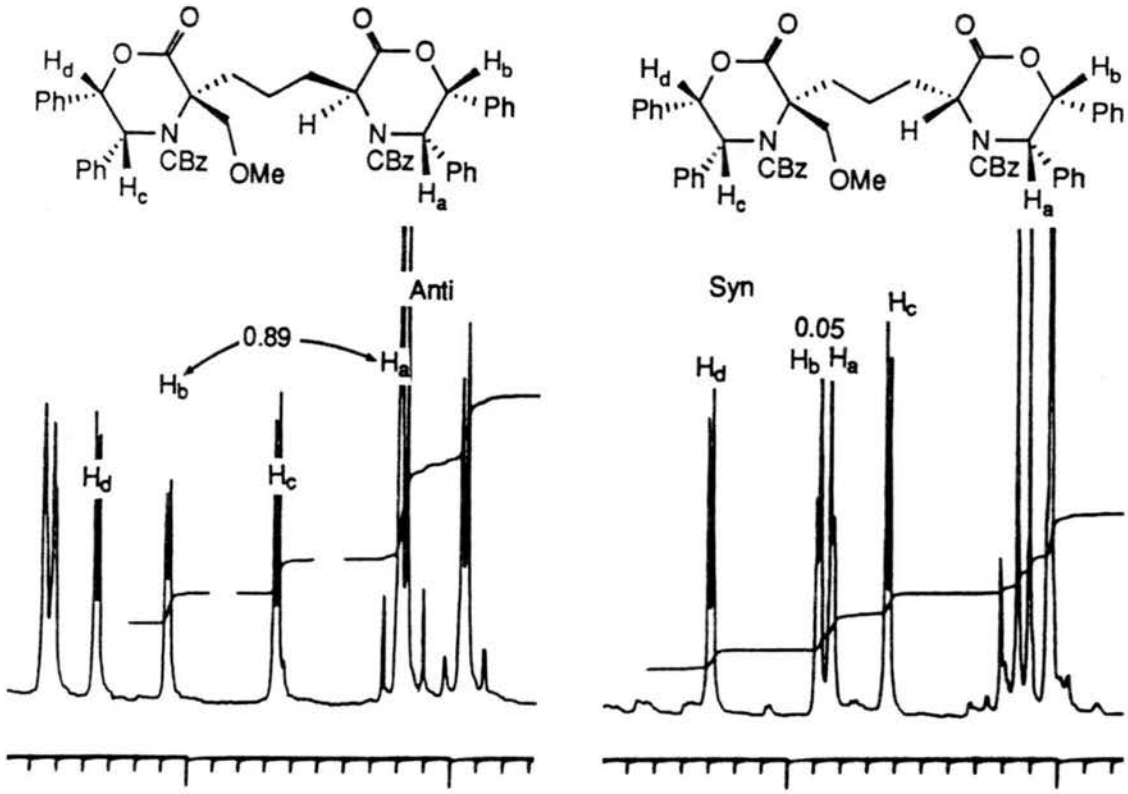


FIGURE 8 Relative $\Delta\delta$ of H_a and H_b for **259**

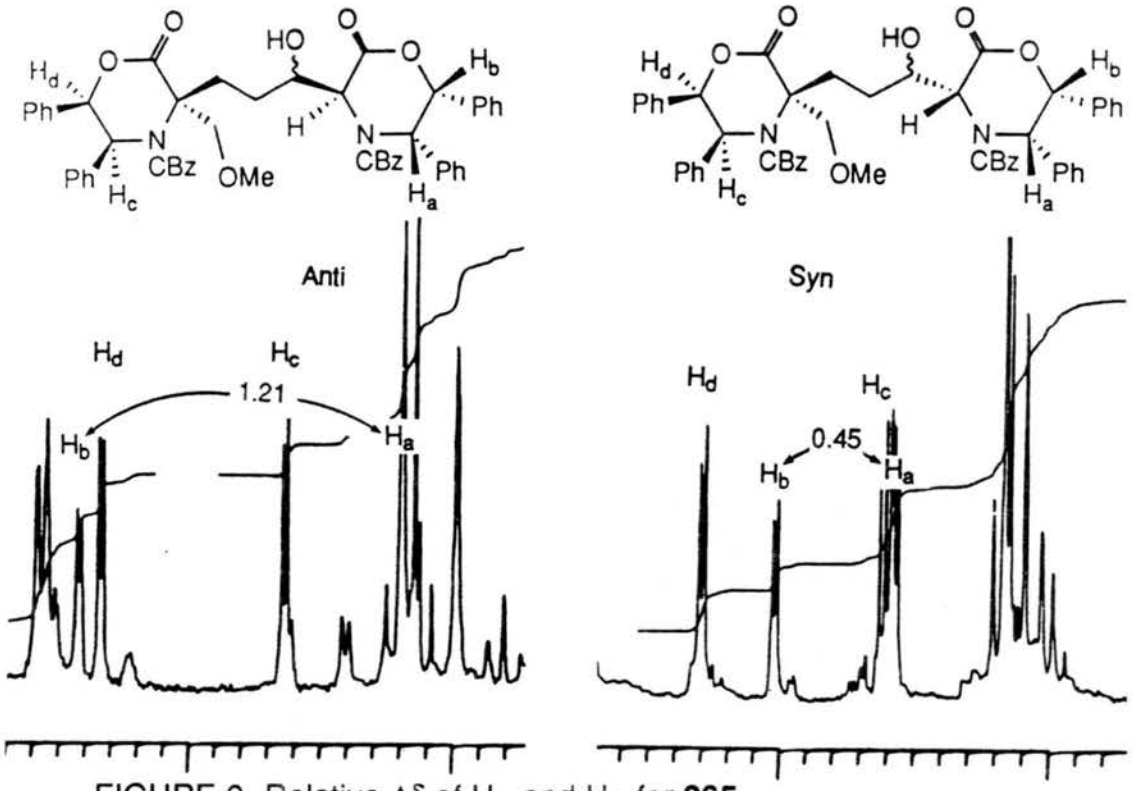


FIGURE 9 Relative $\Delta\delta$ of H_a and H_b for **265**

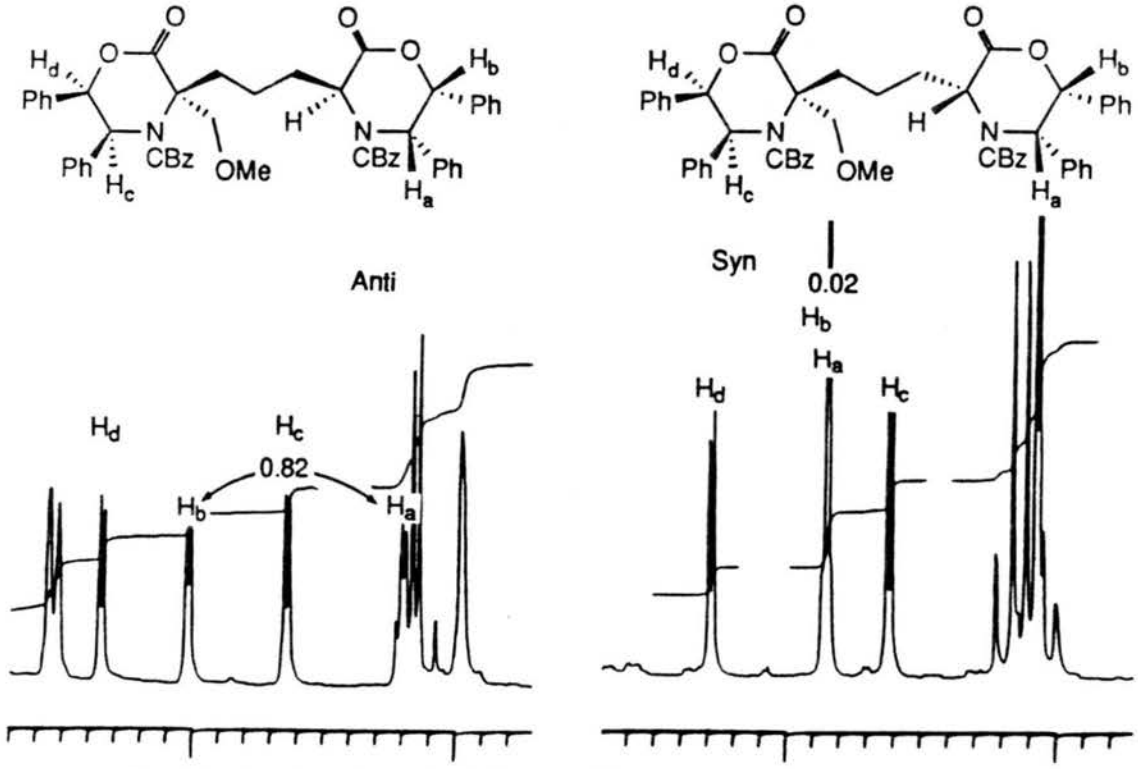
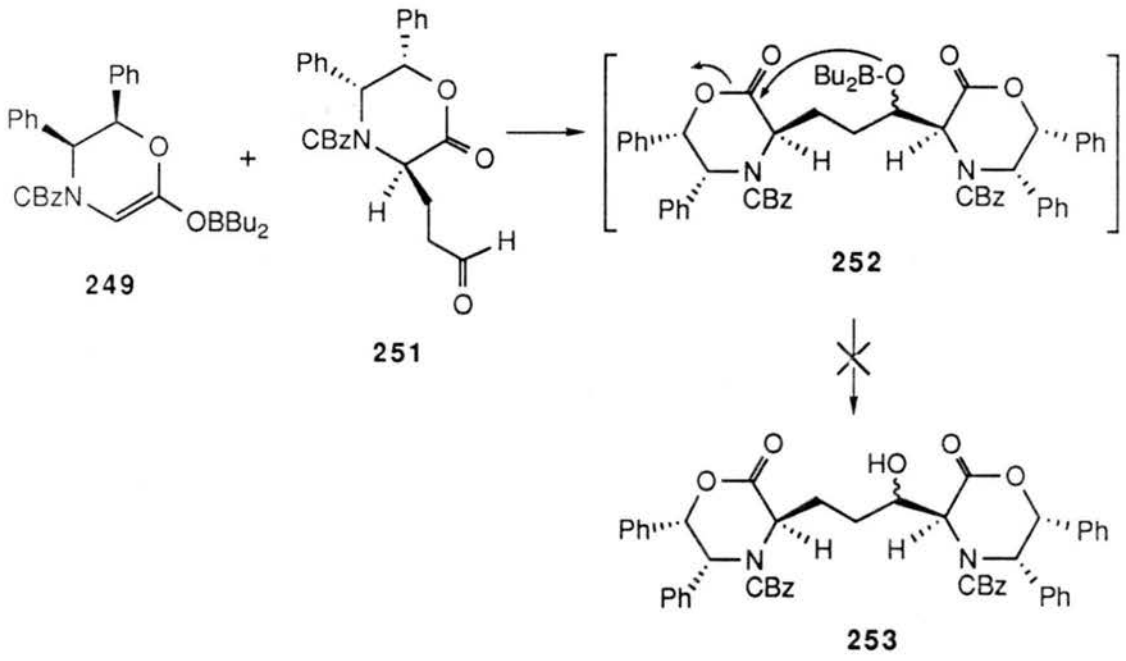


FIGURE 10 Relative $\Delta\delta$ of H_a and H_b for **267**

SCHEME 78



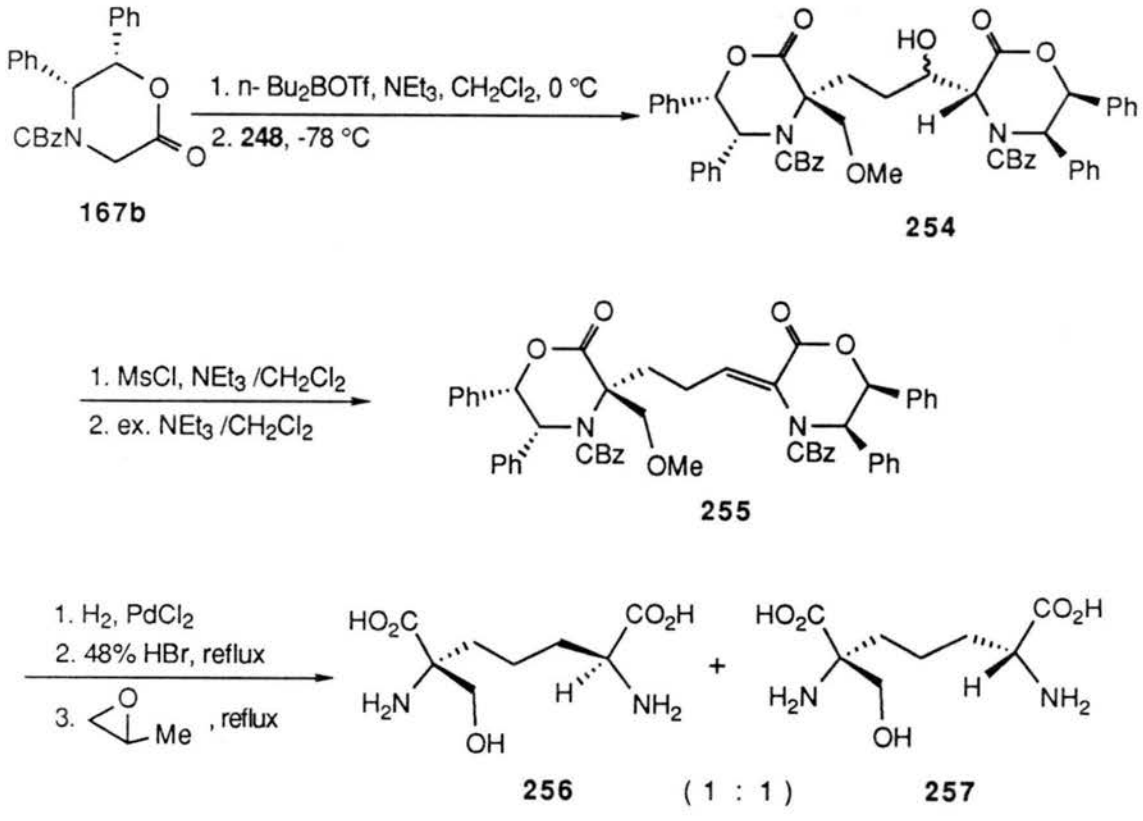
The quaternary aldehyde system **248** undergoes aldol condensation efficiently. Unfortunately, the simple aldehyde **251** does not couple with the oxazinone **167a** under the reaction conditions examined. As shown in Scheme 78, treatment of the aldehyde **251** with the boron enolate **249** did not lead to the desired product **253**. We suspect that the initially formed hydroxy anion attacks the lactone carbonyl carbon derived from **251** to make a labile six-membered ring compound that subsequently decomposes. In the more hindered system **248**, this attack does not occur or proceeds too slowly to be deleterious. Therefore, DAP cannot be readily prepared by this protocol. The t-BOC protected oxazinone (**166**) also does not undergo aldol condensation presumably due to the lability of the t-BOC group to the strong Lewis acid nBu_2BOTf.

Next we examined reductive functional transformation of the hydroxy group to obtain the requisite deoxygenation product. This proved to be very difficult since this alcohol moiety is very hindered and is prone to α,β-

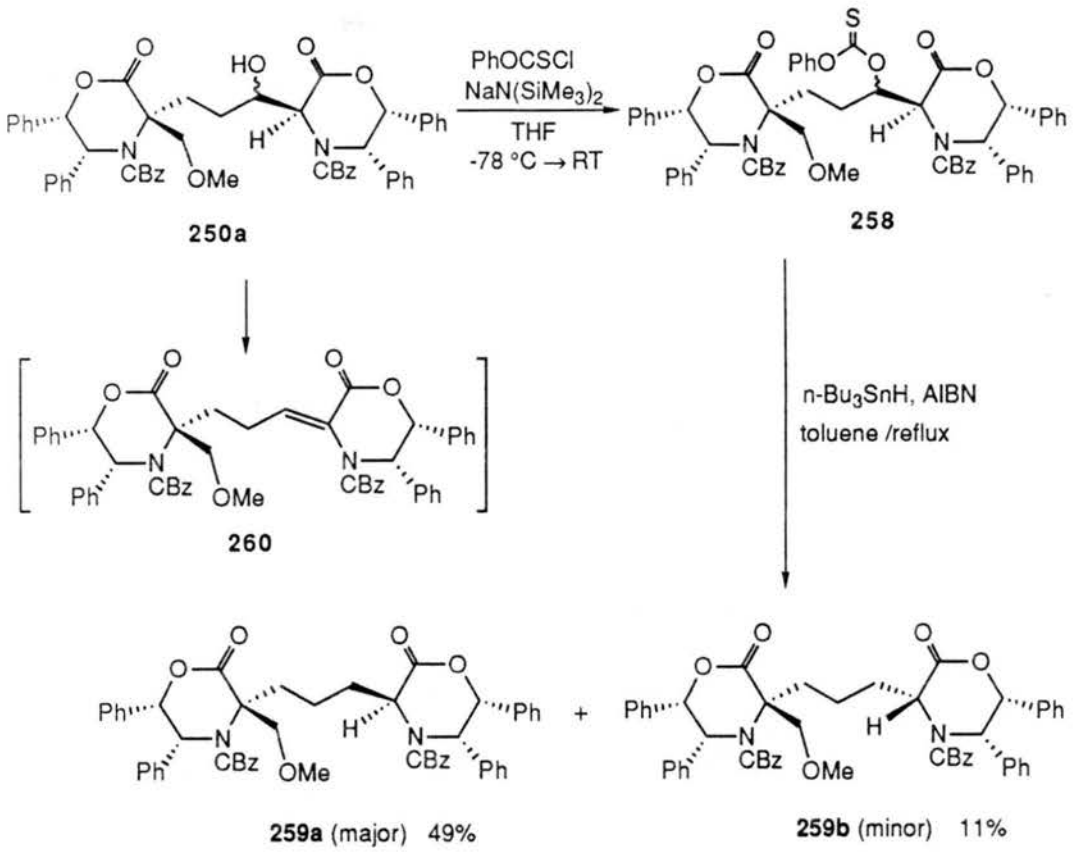
elimination. Many attempts at activating the hydroxyl for hydride displacement resulted in either no reaction or α,β-dehydrogenation.

Therefore, alkene **255** was synthesized with the expectation that the olefin might undergo stereoselective hydrogenation. As shown in Scheme 79, the hydroxy dilactone **254** was obtained by aldol condensation of **167b** and **248**. The reaction of **254** with mesyl chloride in the presence of triethylamine and subsequent treatment with excess triethylamine furnished the alkene **255**. Unfortunately, sequential hydrogenation, hydrolytic deprotection of the methyl group and scavenging of acid with propylene oxide produced the amino acids **256** and **257** as a 1:1 *mixture* of diastereomers.

SCHEME 79

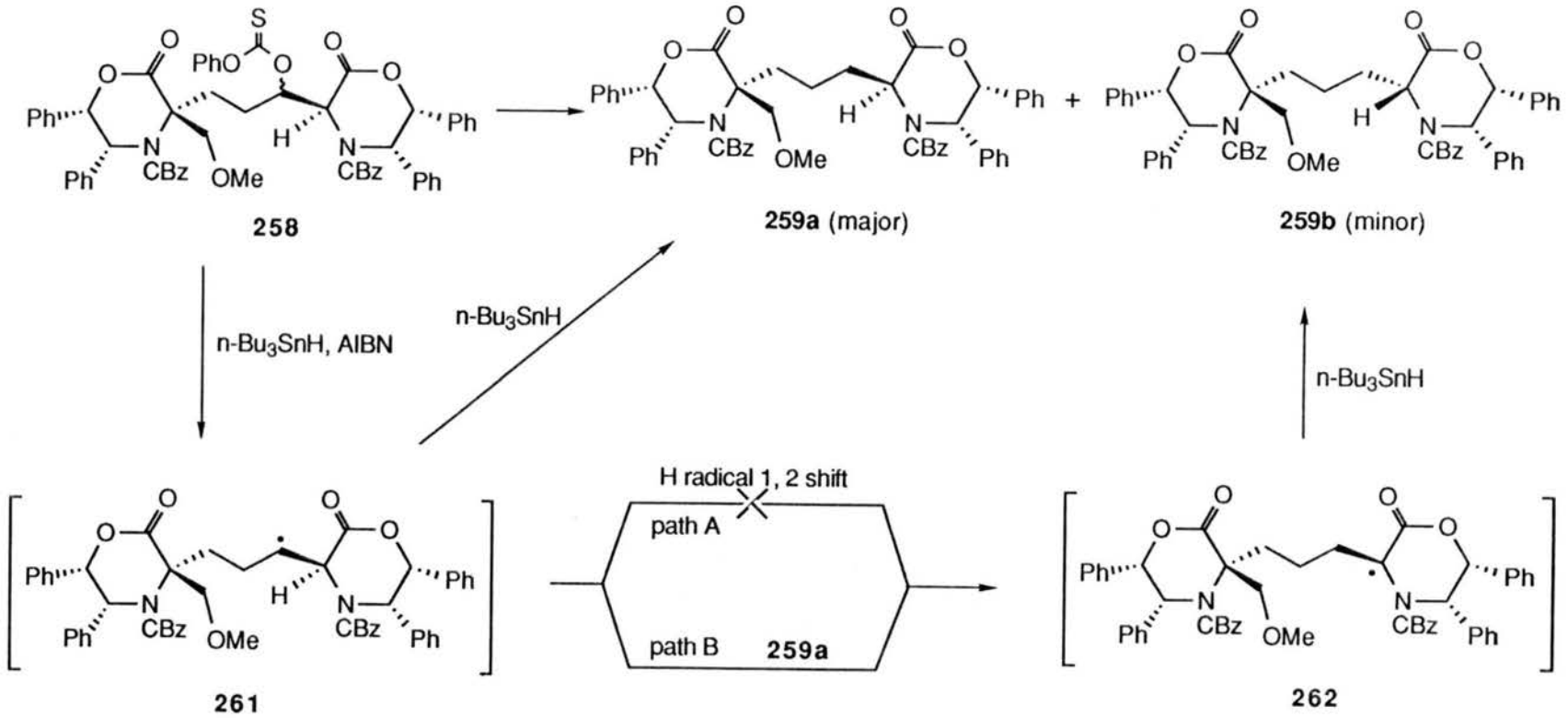


SCHEME 80



This unexpected result forced us to reexamine the deoxygenation of **250a**. After many trials, we established conditions to prepare a Barton reaction[74] precursor. As shown in Scheme 80, treatment of the alcohol **250a** with phenyl chlorothionoformate in the presence of sodium bis(trimethylsilyl)amide furnished the thionoformate **258** in 62% yield. Standard procedures[75] to prepare phenyl thionoformates afforded either the α,β-unsaturated lactone (**260**) or unreacted starting material depending on the reaction conditions. Several attempts to prepare other Barton reaction precursors failed leading to no reaction. Among several bases examined, ($nBuLi$, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_3$, $KN(SiMe_3)_2$), sodium bis(trimethylsilyl)amide gave the best result for the conversion of **250a** → **258**.

SCHEME 81


258
259a (major)
259b (minor)
n-Bu3SnH, AIBN
n-Bu3SnH
n-Bu3SnH
H radical 1, 2 shift
path A
path B
259a
261
262

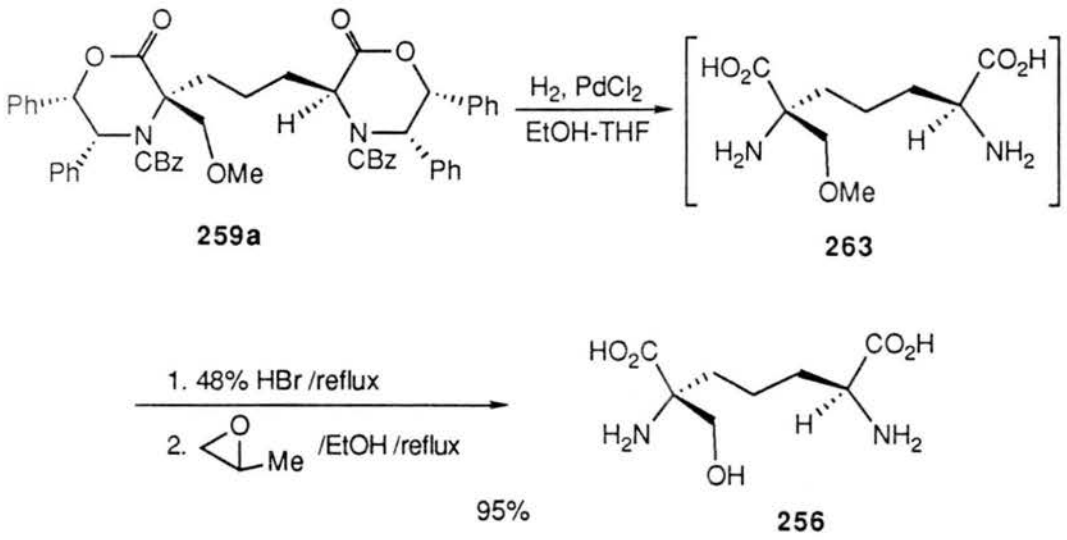
The reduction of **258** with tributyltin hydride in the presence of AIBN in refluxing toluene provided the deoxygenated product **259** in 60% yield (major : minor = 49 : 11).

Formation of the unexpected minor isomer **259b** can be explained mechanistically as follows: As shown in Scheme 81, the initially formed radical **261** is quenched with tributyltin hydride to afford the major diastereomer **259a**. However, the more stable tertiary radical **262** can be formed by two pathways; 1) 1,2-hydrogen migration of the radical; 2) abstraction of the C-3 hydrogen in the initially formed dilactone **259a** by the radical **261**. Hydrogen atom transfer from tributyltin hydride to the tertiary radical **262** proceeds *anti-* to the phenyl ring leading to the minor product **259b**. However, pathway A is unlikely because 1,2 hydrogen shift of the radical is not allowed by orbital symmetry theory and there is no known literature precedent. Alternative pathway B is more plausible. The radical **261** is more likely to abstract hydrogens in a benzylic position since this would generate the more stable benzylic radicals. This process, however, does not impact on the formation of the minor product **259b** resulting in reformation of the major diastereomer **259a** by attack *anti-* to the adjacent phenyl group.

Finally, **259a** was smoothly converted into HMDAP **256**. As shown in Scheme 82, **259a** was hydrogenated to give the amino acid **263** which was converted *in situ* into HMDAP (**256**) in 95% yield by demethylation in refluxing 48% HBr and subsequent scavenging of HBr with propylene oxide in refluxing ethanol.

Measurement of the specific optical rotation indicates that **256** is the compound with the wrong stereochemistry; $[\alpha]^{25}_{D}$ +22.5° (c 0.6, 5N HCl); lit.[65] $[\alpha]^{25}_{D}$ +8.1 ± 1.0° (c 0.506, 5N HCl).

SCHEME 82

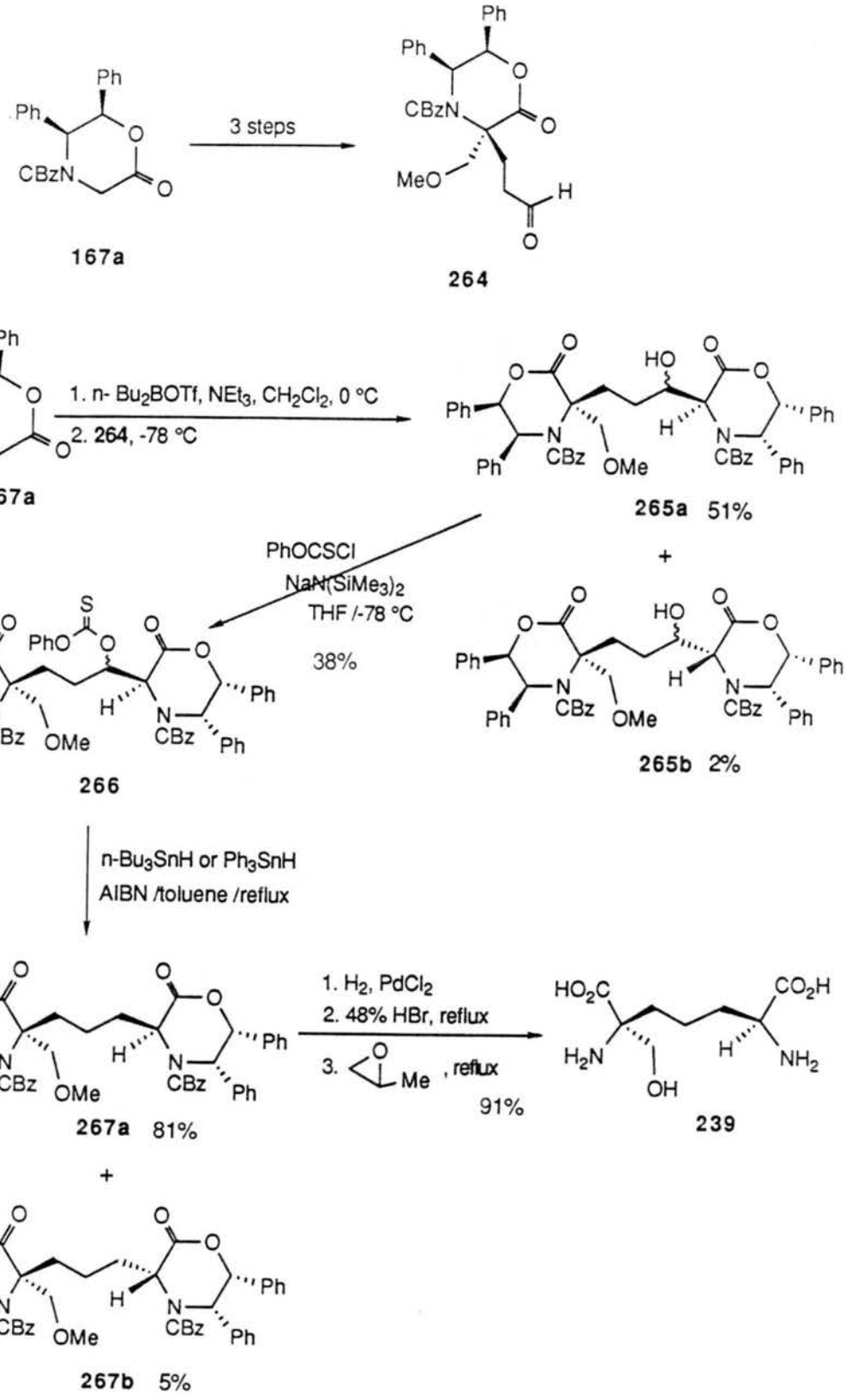


259a **263** **256**

The other diastereomer **239** was prepared in the same manner. As shown in Scheme 83, the aldehyde **264** was obtained from the lactone **167a**. Aldol condensation of **167a** with **264** provided the hydroxy dilactone **265a** as the major diastereomer (51%) plus **265b** as the minor isomer(2%). The major isomer **265a** was converted into the thionoformate **266** by the method described above for **250a**. The reduction of **266** with tributyltin hydride gave the dilactone **227a** (60%) with *anti-* relative stereochemistry to the two phenyl rings at the C-α stereogenic center derived from **167a**. Minor *syn-* isomer **267b** was obtained in 10% yield. The employment of triphenyltin hydride instead of n-Bu_3SnH enhanced the yield remarkably; the major isomer (**267a**) was obtained in 81% yield and the minor (**267b**) in 5.3%. Final deprotection produced HMDAP **239** in 91% yield. Measurement of specific rotation shows that **239** is the compound with the right stereochemistry; $[\alpha]^{25}_D$ +7.1° (C 0.55, 5N HCl).

Using this approach, we can prepare the four diastereomeric HMDAP's, respectively, by employing four possible combinations of enantiomorphic oxazinones **167a/b** and aldehyde **248/264** in the aldol condensation step.

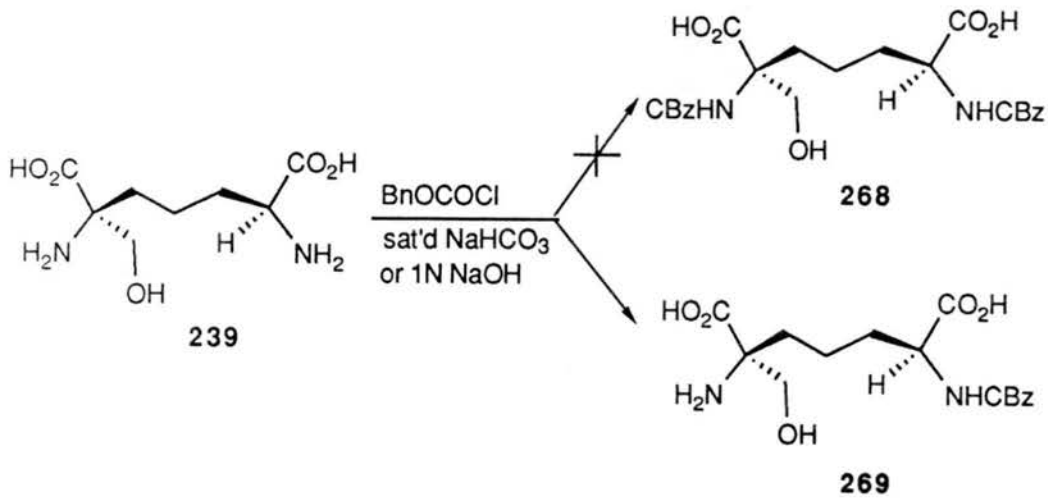
SCHEME 83


3 steps
167a
264
1. n- Bu2BOTf, NEt3, CH2Cl2, 0 °C
2. 264, -78 °C
265a 51%
+
265b 2%
PhOCSCl
NaN(SiMe3)2
THF /-78 °C
38%
266
n-Bu3SnH or Ph3SnH
AIBN /toluene /reflux
1. H2, PdCl2
2. 48% HBr, reflux
3. , reflux
91%
239
267a 81%
+
267b 5%

With the development of an asymmetric path to HMDAP, synthesis of the 2,6-diaminopimelic acid derivatives, which might be potent enzyme inhibitors related to the DAP biosynthetic pathway, is very promising. For instance, aziridine DAP (**245**), an extremely potent inhibitor of DAP-epimerase, can be synthesized in diastereomeric pure forms by hydroxymethyl functional group transformation. This work is under study in Professor Williams laboratories.

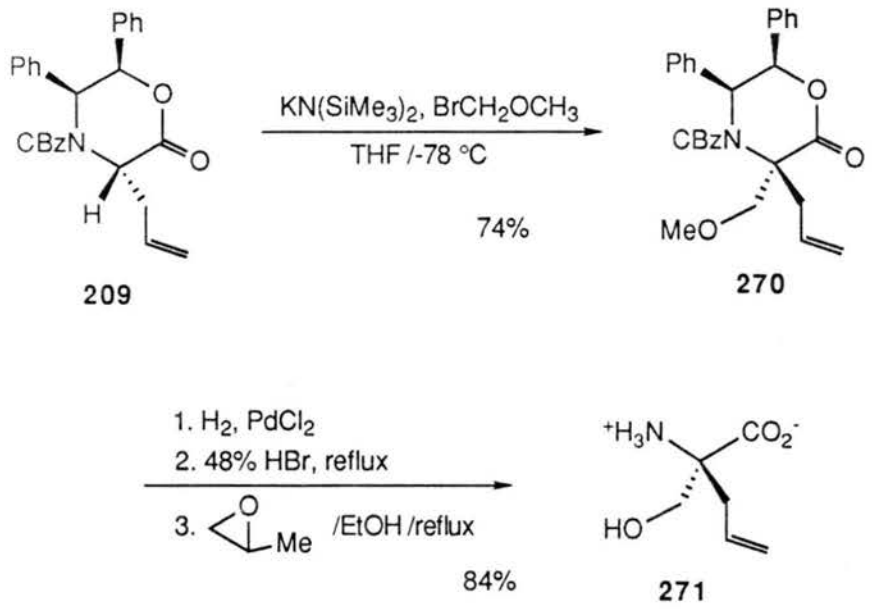
Finally, we examined the coupling reaction to obtain the dipeptide **238**. As shown in Scheme 84, protection of the amino groups was attempted. Treatment of **239** with benzyl chloroformate in the presence of sodium bicarbonate or sodium hydroxide did not produce the diprotected HMDAP **268**. Instead, the monoacylated HMDAP **269** at the less hindered nitrogen was observed by crude NMR but its isolation from the reaction mixture has not yet been achieved.

SCHEME 84



To study masking of the amino group on the hindered side the serine derivative **271** was prepared as a model compound. As shown in Scheme 85, treatment of **209** with bromomethyl methyl ether in the presence of

SCHEME 85



209 270 271

potassium bis(trimethylsilyl)amide produced the allyl methoxymethyl oxazinone **270** which was smoothly converted into the amino acid **271** by standard procedures mentioned above.

Several attempts to protect **271** with a CBz group by various conditions was not successful. Therefore, the relatively small formyl group was examined as a protecting group. The sterically unhindered formyl group is advantageous over other protecting groups; it readily reacts even with less nucleophilic, very conjested amines and alcohols and its selective removal is possible. A long time ago, the formyl group was introduced as a protecting group in peptide synthesis. Several research groups employed the formyl group for blocking the α-nitrogen of amino acids. However, it is not useful for masking amino acids with hydroxy or thiono groups.

We expected concomitant formylation of both the amino and hydroxy groups and subsequent selective removal of the more labile formate. Unfortunately, treatment of the amino acid **271** with acetic formic anhydride or acetic anhydride in formic acid gave rise to a complex reaction mixture. The

failure to protect the amino group on the hindered side made the study of further coupling reactions to obtain the natural product **238** very difficult. Protection of the amine functionality in α-disubstituted amino acids (particularly amino acids with β- or γ-hydroxy groups which are prone to intramolecular reaction leading to eventual complication) should be investigated.

CHAPTER 5

EXPERIMENTAL SECTION

A. General Information

^{1}H NMR spectra were obtained on the following instruments: Brucker WP-200SY 200 MHz Spectrometer, Brucker WP-270SY 270 MHz Spectrometer or Brucker AC 300 MHz spectrometer. ^{19}F NMR spectra were recorded on the Brucker WP-200 SY 200 MHz Spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard.

Infrared spectra were recorded on Perkin-Elmer 1600 Series FTIR and are reported as λ_{max} in cm^{-1}.

Melting points were determined in open-ended capillary tubes on a "Mel-Temp" apparatus and uncorrected.

Optical rotations were obtained on a Rudolph Research Autopol ® III Automatic Polarimeter at wavelength 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1 ml. Specific rotations, $[\alpha]_D$ are 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.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

High resolution mass spectra were carried out by Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska.

B. Chromatography

Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light, I_2 developing chamber and/or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column chromatography was performed using Merck silica gel grade 60, 230-400 mesh, 60Å. Radical chromatography was done on 1, 2 and 4 mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron Model 7924.

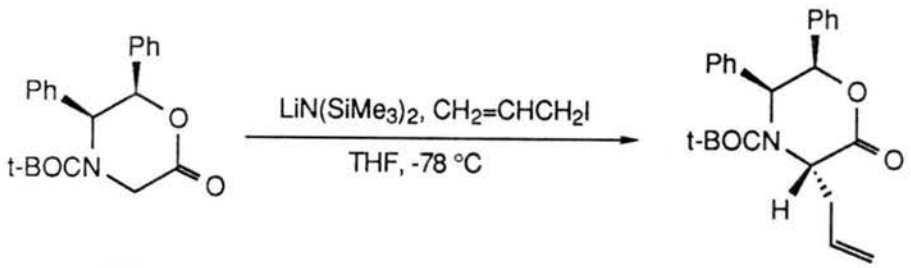
C. Reagents and Solvents

Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dry methylene chloride and carbon tetrachloride were obtained by distillation over CaH_2. DMF and HMPA were dried over activated 4Å molecular sieves.

D. General Experimental Considerations

All moisture sensitive reactions were carried out in glassware that was flame-dried under high vacuum (0.5-2.0 mmHg) and then purged with N_2. All reactions were magnetically stirred with Teflon coated stirring bars. The following low temperature baths were used: 0 °C (ice water), -78 °C (acetone, dry ice), -82 °C (ethyl ether, dry ice). The term "concentrated" refers to solvent removal using a Buchi Rotavapor.

The amino acids furnished crude from the hydrogenation were always obtained in greater than the theoretical amount due to a certain fraction of HCl salt resulting from the $PdCl_2$ catalyst. To ascertain the exact amount of amino acid by weight in the residue, the mixture was dissolved in D_2O with a known amount of terleucine (purity titrated against ultrapure acetamide), and ^1H NMR integration of a well-resolved resonance of the amino acid against the nine-proton singlet of terleucine was carried out, averaged, and calculated to give the adjusted chemical yields.



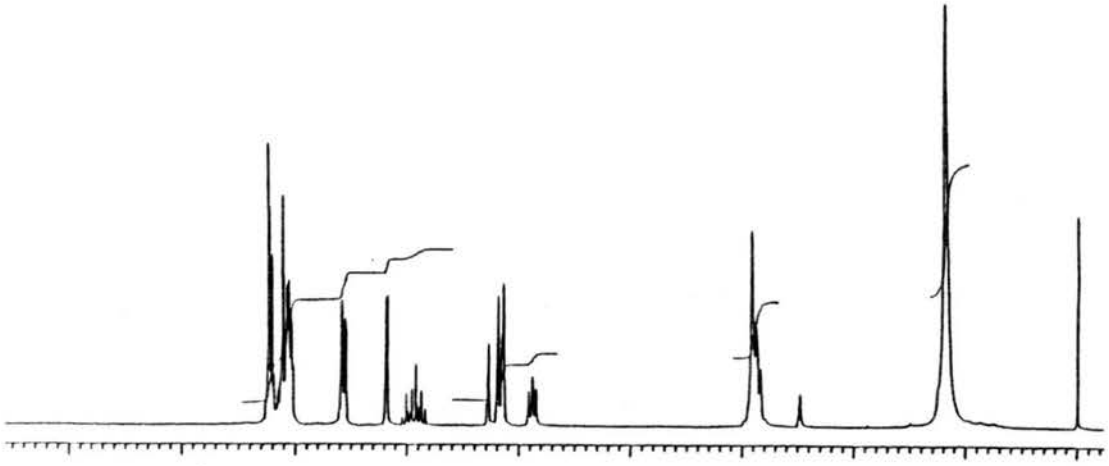
166a **190**

(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-(2'-propenyl) -2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (190)

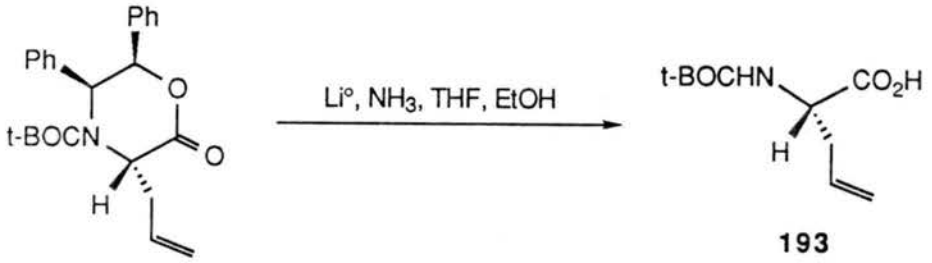
To a stirred solution of **166a** (300 mg, 0.849 mmol, 1 equiv) and allyl iodide (388 µl, 4.243 mmol, 5 equiv) in THF (5 ml) was added lithium bis(trimethylsilyl)amide (1.02 ml, 1.02 mmol, 1.2 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 40 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 286 mg (85.6%) of **190** as white solid and 15.7 mg (5.2%) of unreacted **166a**.

^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.29 (9H, s), 2.82-2.92 (2H, m), 4.88 (1H, t, J = 7.00 Hz), 5.16-5.30 (3H, m), 5.84-6.05 (1H, m), 6.18 (1H, d, J = 3.07 Hz), 6.55-6.59 (2H, m), 7.03-7.27 (8H, m); IR (NaCl, CH_2Cl_2)

1755, 1690 cm^{-1}; mp 178-179 °C, Lit.[49b] 177-178 °C; $[\alpha]^{25}_D$ -48° (c 0.1, CH_2Cl_2), Lit.[49b] -45.8° (c 1.34, CH_2CL_2).



^1H NMR of **190** in DMSO-d_6 at 393 °K



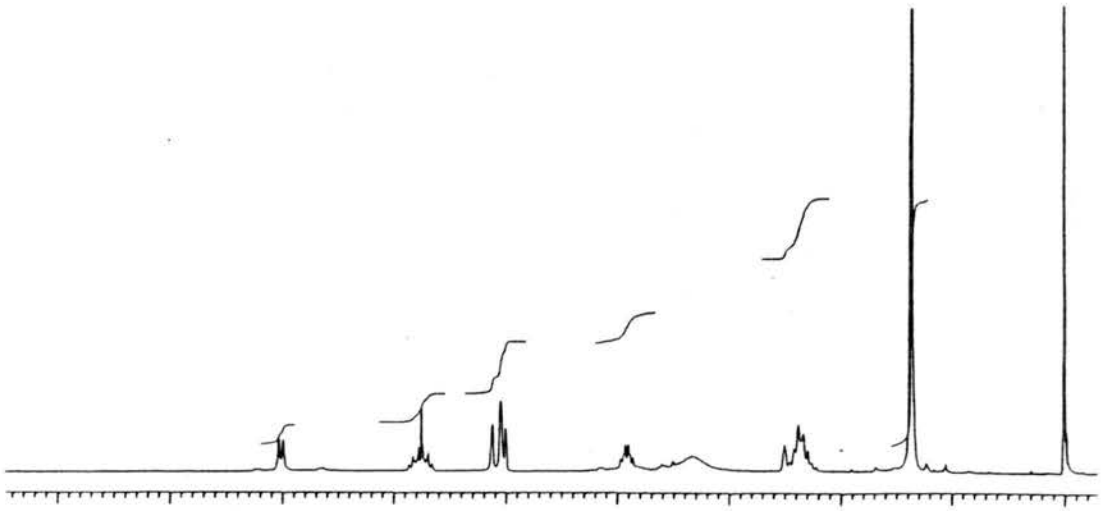
190 **193**

(S)-N-(tert-Butyloxycarbonyl)allylglycine (193)

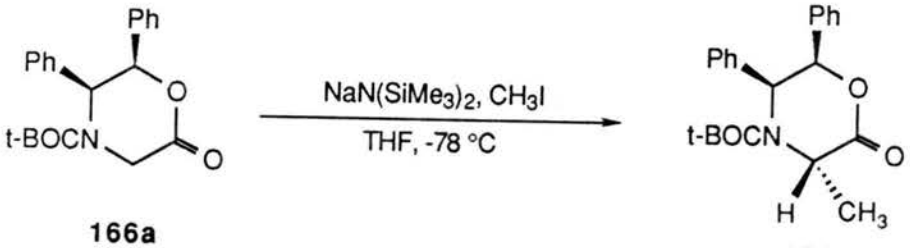
To a solution of Li° (14 mg, 2.017 mmol, 12 equiv) in liquid ammonia (20 ml, distilled from Na°) was added a solution of **190** (66 mg, 0.168 mmol, 1 equiv) and ethanol (120 µl) in THF (3ml) at -33 °C. After 10 min the blue color dissipated, and the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm to ambient temperature. The ammonia was allowed to evaporate off, and the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 2 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium

sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 18 mg (50%) of **193** as colorless oil: 98 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.37 (9H, s), 2.27-2.46 (2H, m), 3.85-3.97 (1H, m), 5.01-5.14 (2H, m), 5.67-5.87 (1H, m), 7.01 (1H, d, D_2O exch., J = 8.04 Hz); IR (NaCl, $CDCl_3$) 3430, 3050, 1715 cm^{-1}; $[\alpha]^{25}_D$ -3.9° (c 1, CH_2Cl_2), Lit.[49b] -3.8° (c 1.5, CH_2Cl_2).



^{1}H NMR of **193** in DMSO-d_6 at 295 °K



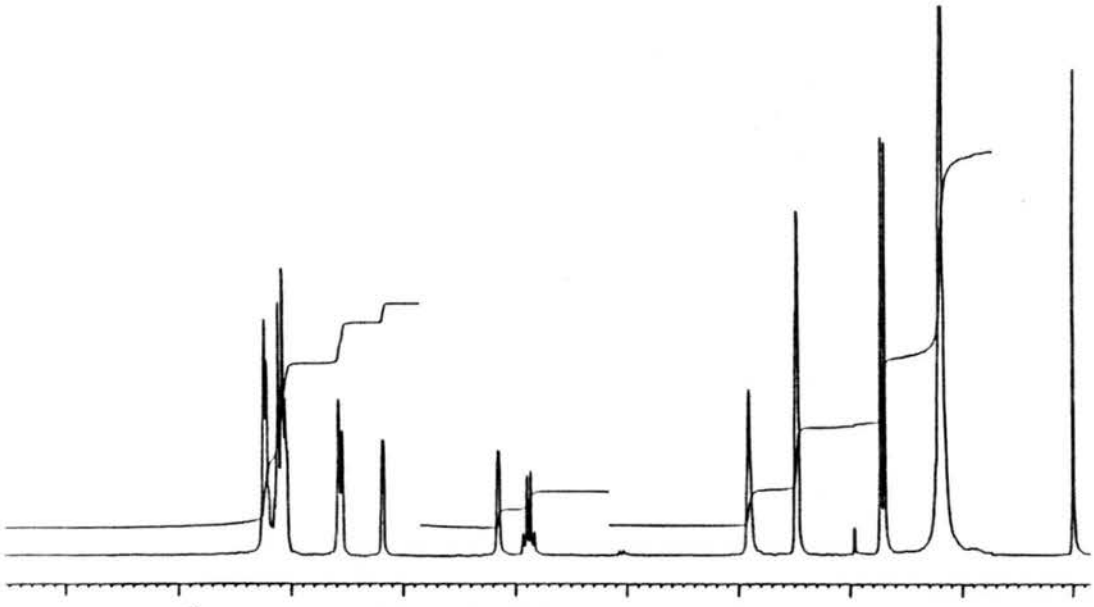
166a **192**

(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (192)

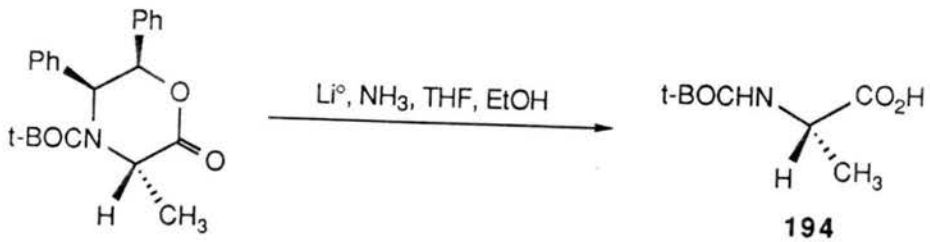
To a stirred solution of **166a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 ml) was added sodium bis(trimethylsilyl)amide (1.5 ml, 1.5 mmol, 1.06 equiv, 1 M solution in THF) dropwise via syringe at -82 °C. After 35 min methyl iodide (900 µl, 14.46 mmol, 10.2 equiv) was added to the reaction mixture. The resulting solution was stirred additional 1.5 hr at -82 °C and poured into water.

The aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by radial chromatography on silica gel to afford 475 mg (91%) of **192** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.19 (9H, s), 1.71 (3H, d, J = 6.99 Hz), 4.88 (1H, q, J = 7.12 Hz), 5.15 (1H, d, J = 2.81 Hz), 6.18 (1H, d, J =2.87 Hz), 6.54 (2H, m), 7.03-7.29 (8H, m); IR (NaCl, CH_2Cl_2) 1752, 1702 cm^{-1}; mp 204-206 °C; $[\alpha]^{25}_D$ -61° (c 0.2, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{22}H_{25}NO_4$: C, 71.93; H, 6.81; N, 3.81. Found: C, 71.89; H, 6.92; N, 3.76.



^{1}H NMR of 192 in DMSO-d_6 at 393 °K

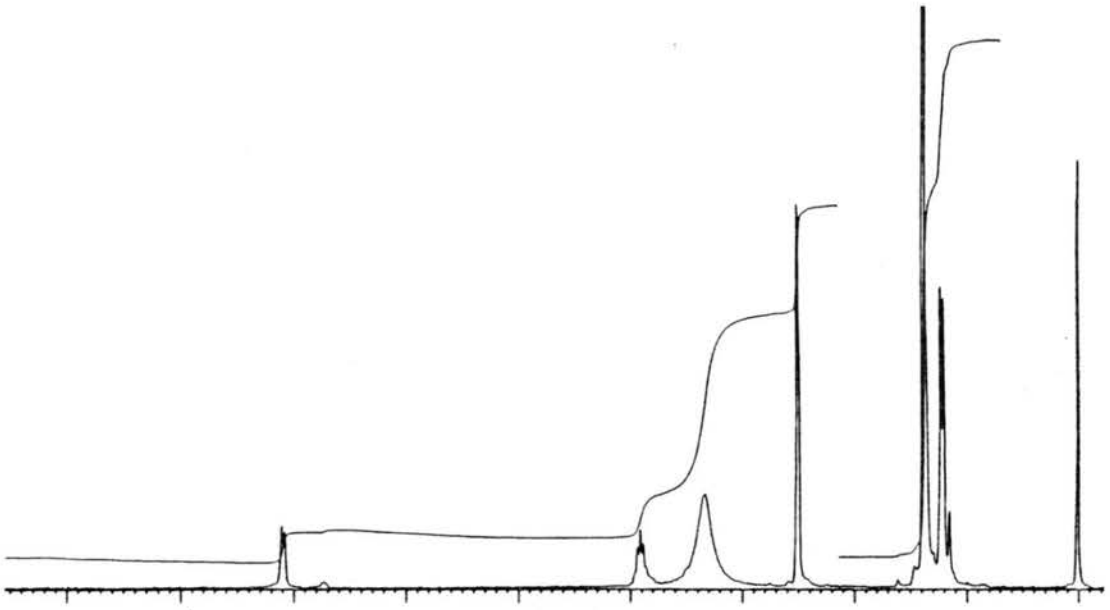


192 **194**

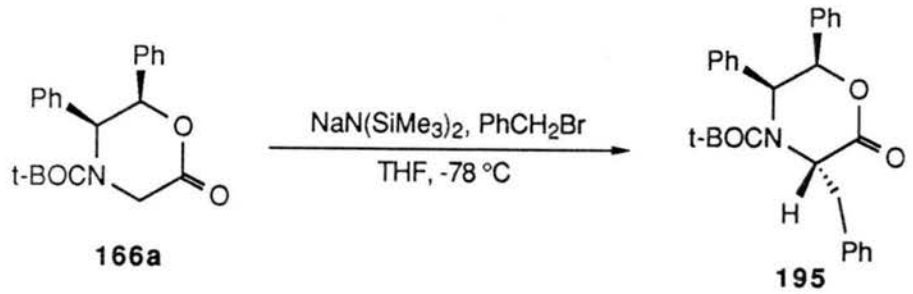
(S)-N-(tert-Butyloxycarbonyl)alanine (194)

To a solution of Li° (14.5 mg, 2.084 mmol, 15 equiv) in liquid ammonia (20 ml, distilled from Na°) was added a solution of **192** (51 mg, 0.139 mmol, 1 equiv) and ethanol (150 µl) in THF (3ml) at -33 °C. After 1 hr the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm to ambient temperature. The ammonia was allowed to evaporate off, and the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 3 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 14 mg (54%) of **194** as white solid: 97.2 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.21 (3H, d, J = 7.34 Hz), 1.37 (9H, s), 3.91 (1H, m), 7.10 (1H, d, D_2O exch., J = 7.60 Hz); IR (NaCl, $CDCl_3$) 3710, 1725, 1708 cm^{-1}; mp 81-82 °C, Lit.[76] 83-84 °C; $[\alpha]^{25}_D$ -15.5° (c 2.75, CH_2Cl_2), Lit.[76] -22.4° (2.1% CH_3CO_2H).



^{1}H NMR of **194** in DMSO-d_6 at 295 °K

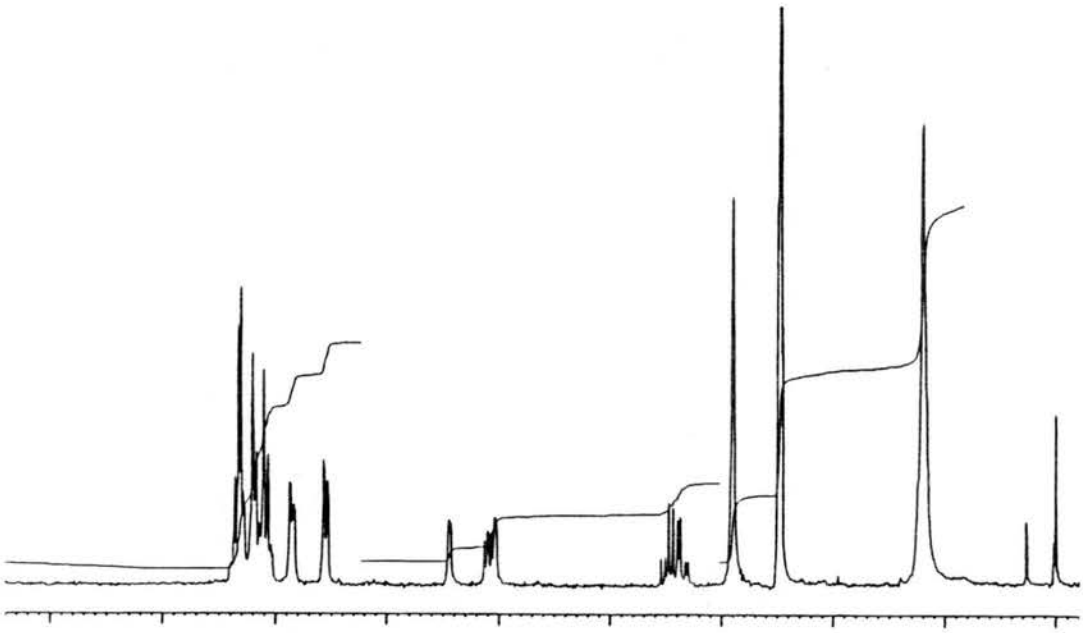


166a **195**

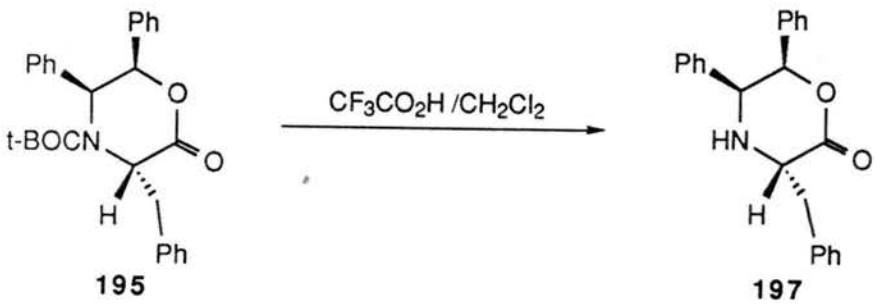
(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-benzyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (195)

To a stirred solution of **166a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 ml) was added sodium bis(trimethylsilyl)amide (1.42 ml, 1.42 mmol, 1 equiv, 1 M solution in THF) dropwise via syringe at -82 °C. After 40 min benzyl bromide (170 µl, 1.43 mmol, 1 equiv) was added to the reaction mixture. The resulting solution was stirred additional 1.5 hr at -82 °C and poured into water. The aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by radial chromatography on silica gel to afford 441 mg (70%) of **195** as white solid and 46 mg (9.2%) of unreacted **166a**.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.19 (9H, s), 3.35 (1H, dd, J = 13.84 Hz, J = 4.67 Hz), 3.48 (1H, dd, J = 13.80 Hz, J = 7.82 Hz), 5.03 (1H, d, J = 2.97 Hz), 5.10 (1H, dd, J =4.91 Hz, J = 4.55 Hz), 5.44 (1H, d, J = 2.51 Hz), 6.53 (2H, m), 6.81-6.89 (2H, m) 7.07-7.39 (11H, m); IR (NaCl, CH_2Cl_2) 1754, 1697 cm^{-1}; mp 147-149 °C; $[\alpha]^{25}_D$ +49° (c 0.2, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{28}H_{29}NO_4$: C, 75.85; H, 6.55; N, 3.16. Found: C, 75.76; H, 6.67; N, 3.05.



^{1}H NMR of **195** in DMSO-d_6 at 393 °K



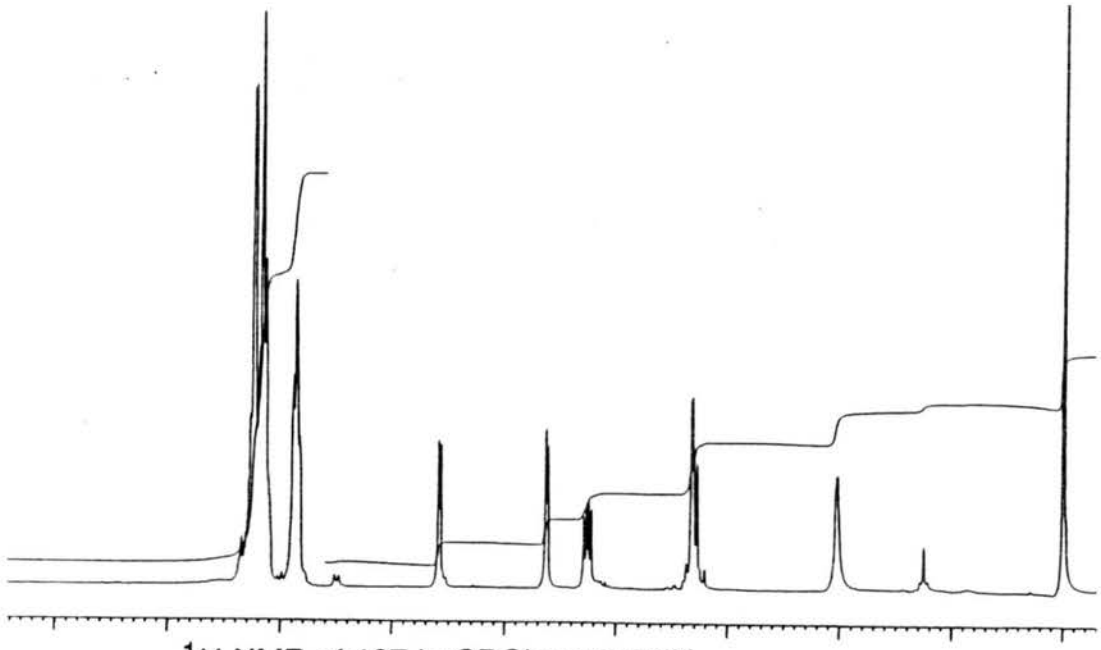
195 **197**

(3S,5S,6R)-5,6-diphenyl-3-benzyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (197)

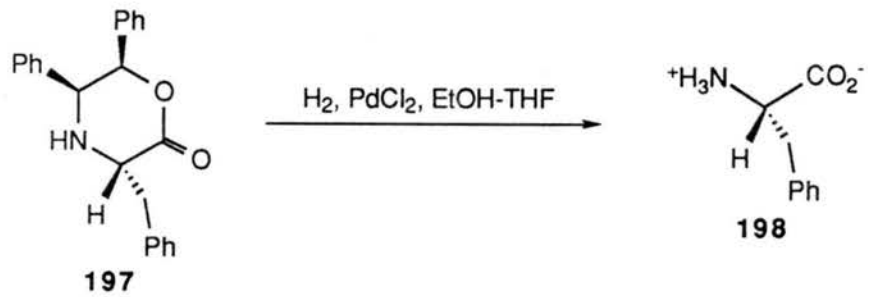
To a stirred solution of **195** (104 mg, 0.235 mmol, 1 equiv) in CH_2Cl_2 (2ml) was added trifluoroacetic acid (200 µl, 2.596 mmol, 11 equiv). After 4 hr

the reaction mixture was neutralized with excess triethyl amine, concentrated and separated by PTLC on silica gel to afford 65 mg (80%) of **197** as colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$, vs TMS) δ 2.01 (1H, s, D_2O exch.), 3.26-3.38 (2H, m), 4.26 (1H, dd, J = 8.56 Hz, J = 4.79 Hz), 4.61 (1H, d, J = 3.64 Hz), 5.58 (1H, d, J =3.63 Hz), 6.80-6.89 (4H, m), 7.11-7.30 (11H, m) ; IR (NaCl, CH_2Cl_2) 3328, 1732 cm^{-1}; $[\alpha]^{25}D$ +91° (c 0.8, CH_2Cl_2).



^{1}H NMR of **197** in $CDCl_3$ at 295 °K



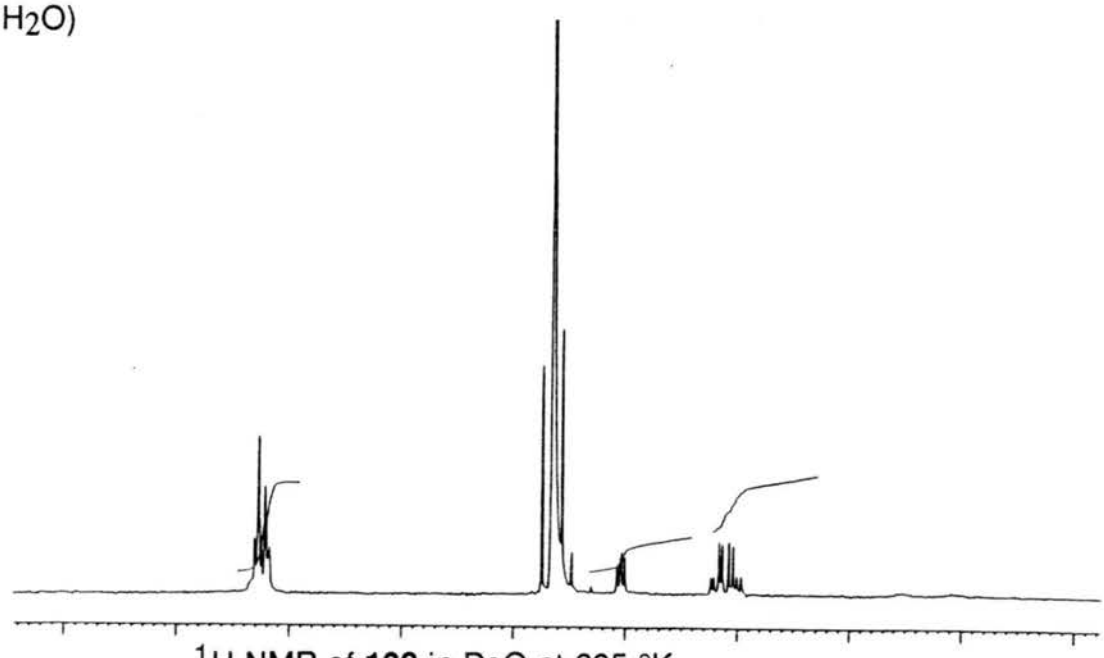
197 **198**

(S)-Phenylalanine (198)

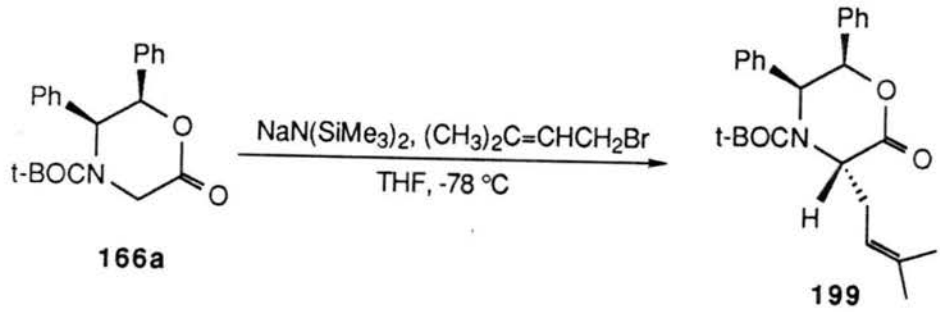
To a solution of **197** (67 mg, 0.195 mmol, 1 equiv) in THF and EtOH (2ml, 1:1) was added palladium chloride (24 mg, 0.135 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 42 psi for 29 hr. The mixture was then

purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 33 mg (102%) of **198** as white solid: 98.2 % ee; adjusted chemical yield 76%.

^1H NMR (200 MHz, D_2O, vs HOD) δ 3.02 (1H, dd, J = 14.92 Hz, J = 7.73 Hz), 3.20 (1H, dd, J = 15.49 Hz, J = 5.54 Hz), 4.05 (1H, dd, J = 7.31 Hz, J = 5.45 Hz), 7.28-7.34 (5H, m); $[\alpha]^{25}_D$ -32° (c 0.1, H_2O), Lit.[77] -33.7 ~ -35.2° (c 2, H_2O)



^1H NMR of **198** in D_2O at 295 °K



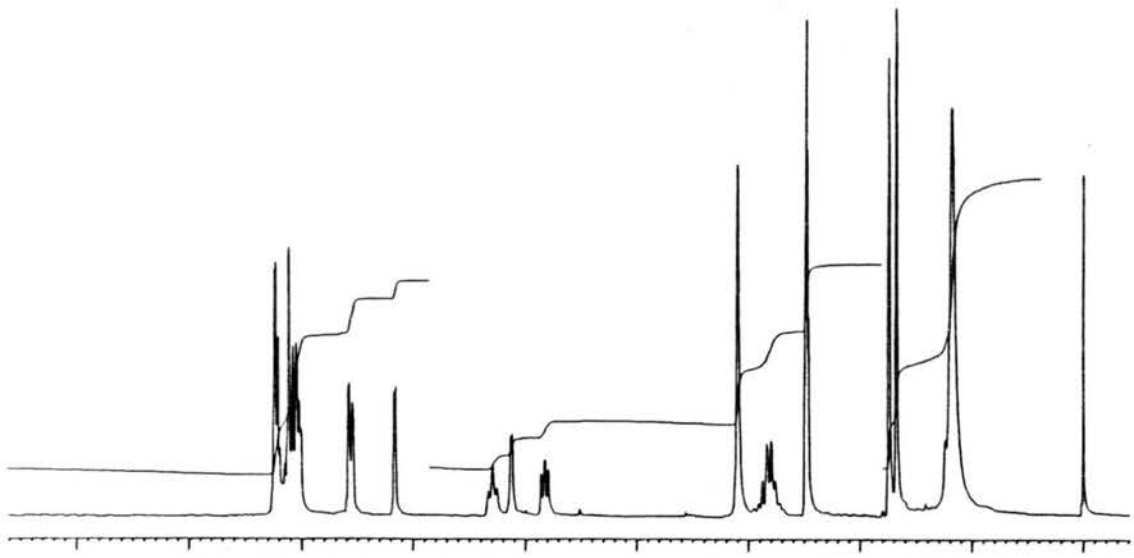
166a **199**

(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-(3'-methyl-2'-butenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (199)

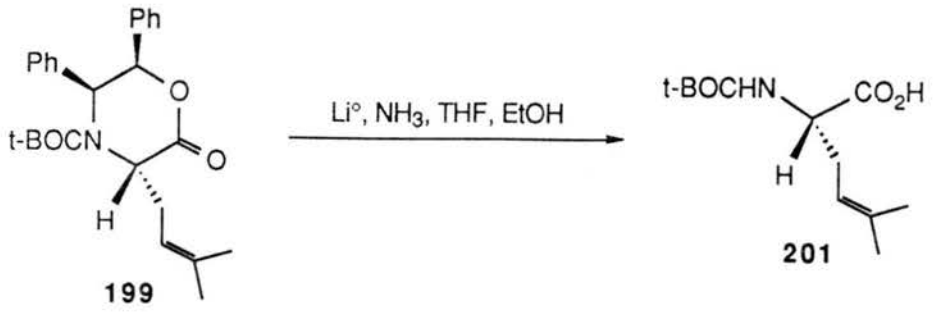
To a stirred solution of **166a** (300 mg, 0.849 mmol, 1 equiv) and 1-bromo-3-methyl-2-butene (493 µl, 4.241 mmol, 5 equiv) in THF (5 ml) was

added sodium bis(trimethylsilyl)amide (934 µl, 0.934 mmol, 1.1 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 30 min the dry ice bath was removed and the reaction mixture was stirred additional 30 min. The reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 302 mg (84.4%) of **199** as white solid and 9.3 mg (2.2%) of dialkylated lactone as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.18 (9H, s), 1.68 (3H, s), 1.74 (3H, s), 2.73-3.01 (2H, m), 4.82 (1H, dd, J = 7.79 Hz, J = 5.64 Hz), 5.12 (1H, d, J =2.75 Hz), 5.30 (1H, t, J = 7.62 Hz), 6.16 (1H, d, J = 3.11 Hz), 6.56 (2H, m), 7.01-7.28 (8H, m); IR (KBr, disc) 1734, 1692 cm^{-1}; mp 150-151 °C; $[\alpha]^{25}_D$ -19.5° (c 0.57, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{26}H_{31}NO_4$: C, 74.11; H, 7.36; N, 3.33. Found: C, 74.24; H, 7.32; N, 3.28.



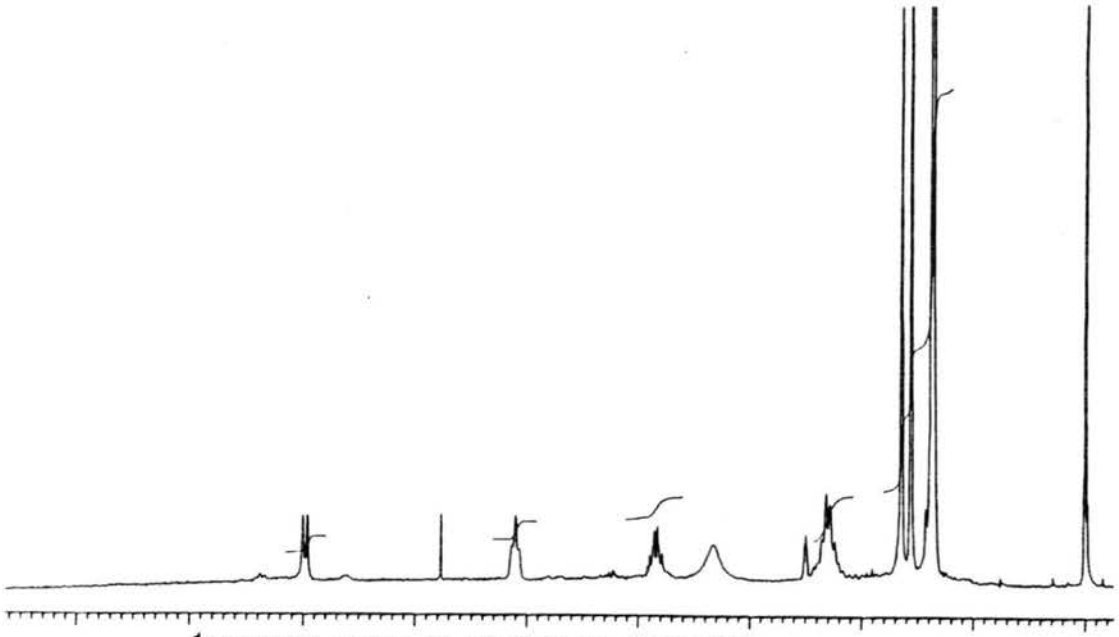
^{1}H NMR of **199** in DMSO-d_6 at 393 °K



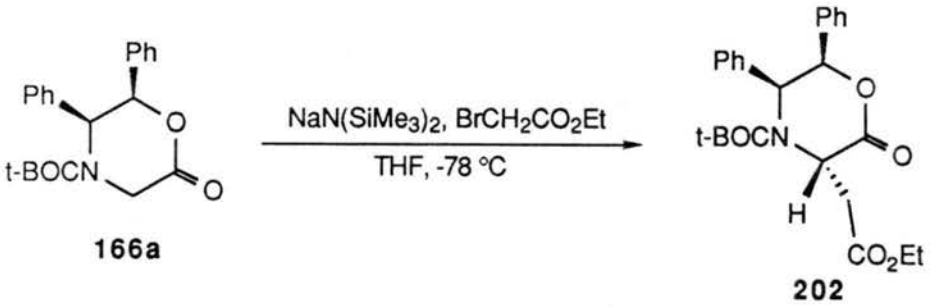
(S)-N-(tert-Butyloxycarbonyl)dimethallylglycine (201)

To a solution of Li° (47 mg, 6.77 mmol, 13 equiv) in liquid ammonia (30 ml, distilled from Na°) was added a solution of **199** (220 mg, 0.52 mmol, 1 equiv) and ethanol (300 µl) in THF (5 ml) at -33 °C. After 1 hr the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm to ambient temperature. The ammonia was allowed to evaporate off, and the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 3 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 66 mg (52%) of **201** as colorless oil: 100 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.37 (9H, s), 1.57 (3H, s), 1.65 (3H, s), 2.19-2.39 (2H, m), 3.77-3.91 (1H, m), 5.08 (1H, t, J = 6.79 Hz), 6.95 (1H, d, D_2O exch., J = 8.07 Hz); IR (NaCl, $CDCl_3$) 3340, 1728, 1700 (shoulder) cm^{-1}; $[\alpha]^{25}_D$ +8.6° (c 0.67, CH_2Cl_2). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.26; H, 8.64; N, 5.76. Found: C, 59.07; H, 8.64; N, 5.62.



^{1}H NMR of **201** in DMSO-d_6 at 295 °K



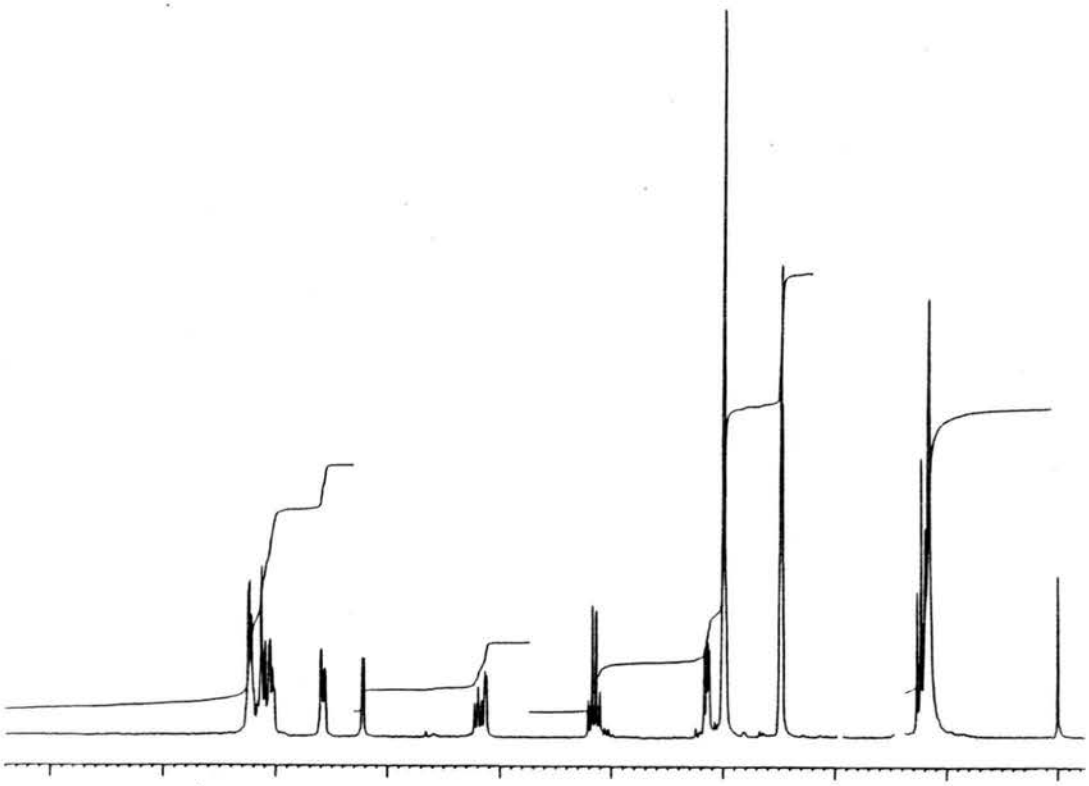
166a **202**

(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-ethoxy-carbonylmethyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (202)

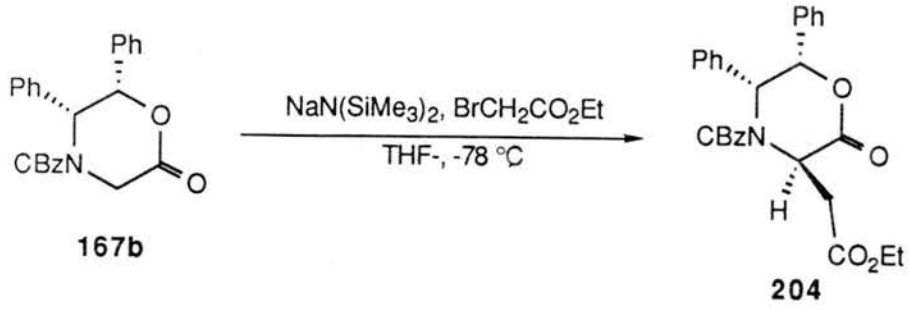
To a stirred solution of **166a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 ml) was added sodium bis(trimethylsilyl)amide (1.42 ml, 1.42 mmol, 1 equiv, 1 M solution in THF) dropwise via syringe at -82 °C. After 40 min ethyl bromoacetate (190 µl, 1.713 mmol, 1.2 equiv) was added to the reaction mixture. The resulting solution was stirred additional 2 hr at -82 °C and poured into water. The aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate,

filtered, concentrated and separated by radial chromatography on silica gel to afford 396 mg (63.7%) of **202** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.18 (9H, s), 1.22 (3H, t, J = 6.96 Hz), 3.12-3.19 (2H, m), 4.16 (2H, q, J = 7.14 Hz), 5.12 (1H, d, J = 2.96 Hz), 5.20 (1H, t, J = 6.73 Hz), 6.20 (1H, d, J = 3.03 Hz), 6.59 (2H, m), 7.00-7.28 (8H, m); IR (NaCl, CH_2Cl_2) 1749, 1739, 1706 cm^{-1}; mp 126-128 °C; $[\alpha]^{25}_D$ -16.3° (c 0.26, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{25}H_{29}NO_6$: C, 68.34; H, 6.61; N, 3.19. Found: C, 68.07; H, 6.49; N, 3.08.



^{1}H NMR of **202** in DMSO-d_6 at 393 °K

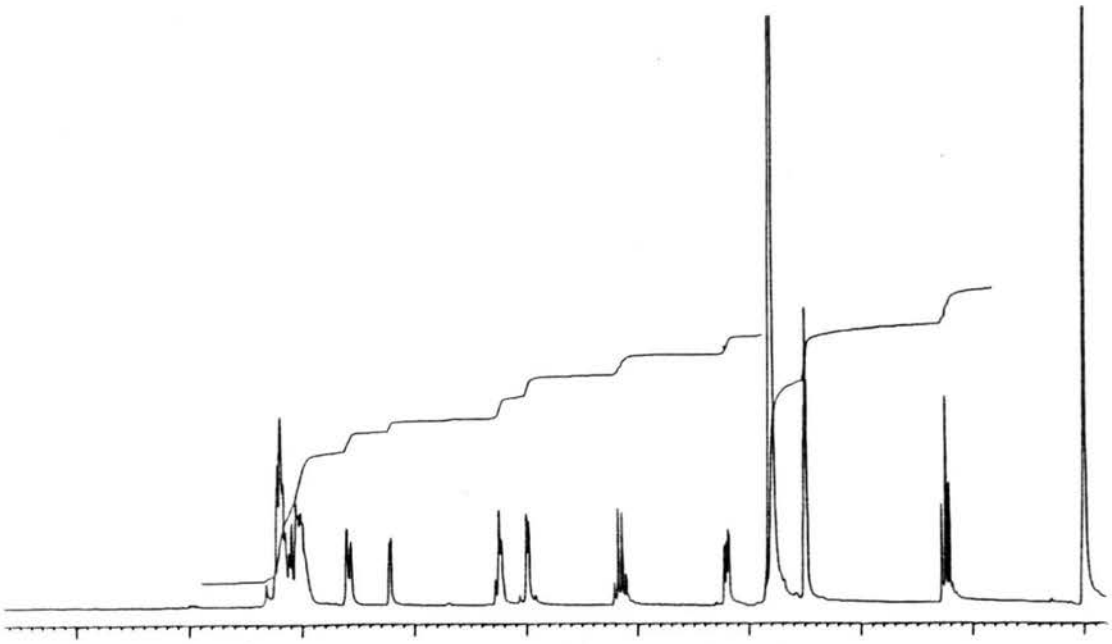


167b **204**

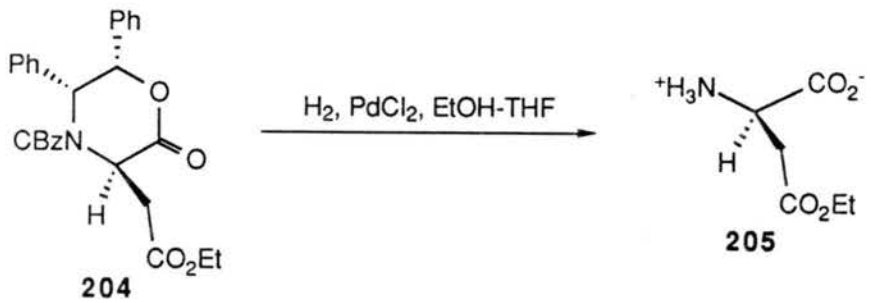
(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-ethoxycarbonyl-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (204)

To a stirred solution of **167b** (500 mg, 1.29 mmol, 1 equiv) in THF (20 ml) was added sodium bis(trimethylsilyl)amide (1.42 ml, 1.42 mmol, 1.1 equiv, 1 M solution in THF) dropwise via syringe at -82 °C. After 40 min ethyl bromoacetate (190 µl, 1.71 mmol, 1.3 equiv) was added to the reaction mixture. The resulting solution was stirred additional 1 hr at -82 °C and poured into water. The aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by radial chromatography on silica gel to afford 373 mg (61%) of **204** as white solid and 102 mg (20.4%) of unreacted **167b**.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.24 (3H, t, J = 7.05 Hz), 3.19 (2H, dd, J = 3.71 Hz, J = 2.34 Hz), 4.15 (2H, q, J = 7.07 Hz), 4.95 (1H, 1/2 ABq, J = 13.52 Hz), 5.04 (1H, 1/2 ABq, J =13.56 Hz), 5.20-5.29 (2H, m), 6.22 (1H, d, J = 3.07 Hz), 6.56-6.63 (2H, m), 6.98-7.27 (13H, m); IR (NaCl, CH_2Cl_2) 1745, 1736, 1707 cm^{-1}; mp 150-151 °C; $[\alpha]^{25}_D$ -2.6° (c 0.5, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{28}H_{27}NO_6$: C, 71.04; H, 5.71; N, 2.96. Found: C, 70.92; H, 5.71; N, 2.96.



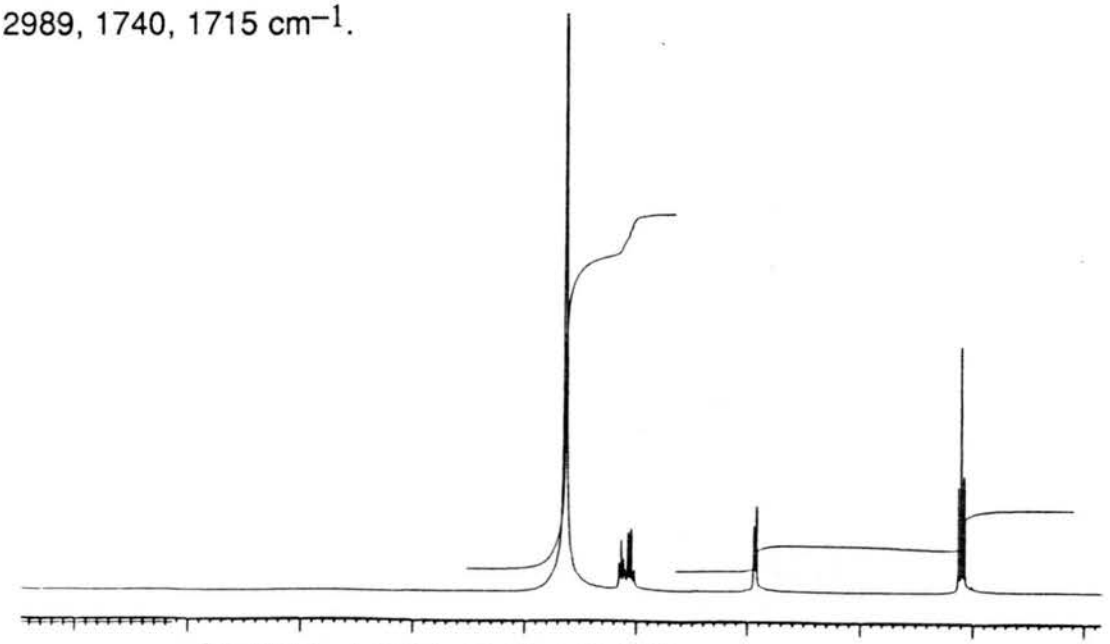
^{1}H NMR of **204** in DMSO-d_6 at 393 °K



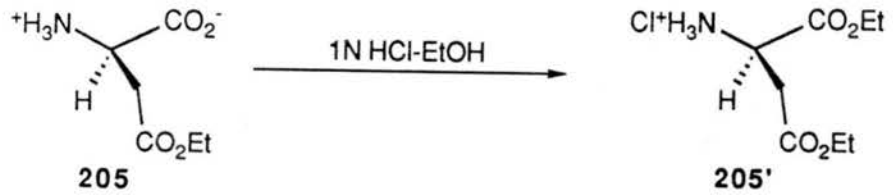
(R)-β-Ethyl Aspartic Acid (205)

To a solution of **204** (135 mg, 0.28 mmol, 1 equiv) in THF and EtOH (1.5 ml, 1:2) was added palladium chloride (35 mg, 0.20 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 50 psi for 24 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 48 mg (104%) of **205** as white solid. This material was used without further purification for the next step: 95.9 % ee; adjusted chemical yield 71%.

^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.10 (3H, t, J = 7.12 Hz), 2.93 (2H, d, J = 5.43 Hz), 4.05 (2H, q, J = 7.07 Hz), 4.24 (1H, t, J = 5.67 Hz); IR (KBr, disc) 2989, 1740, 1715 cm^{-1}.



^{1}H NMR of **205** in D_2O at 295 °K

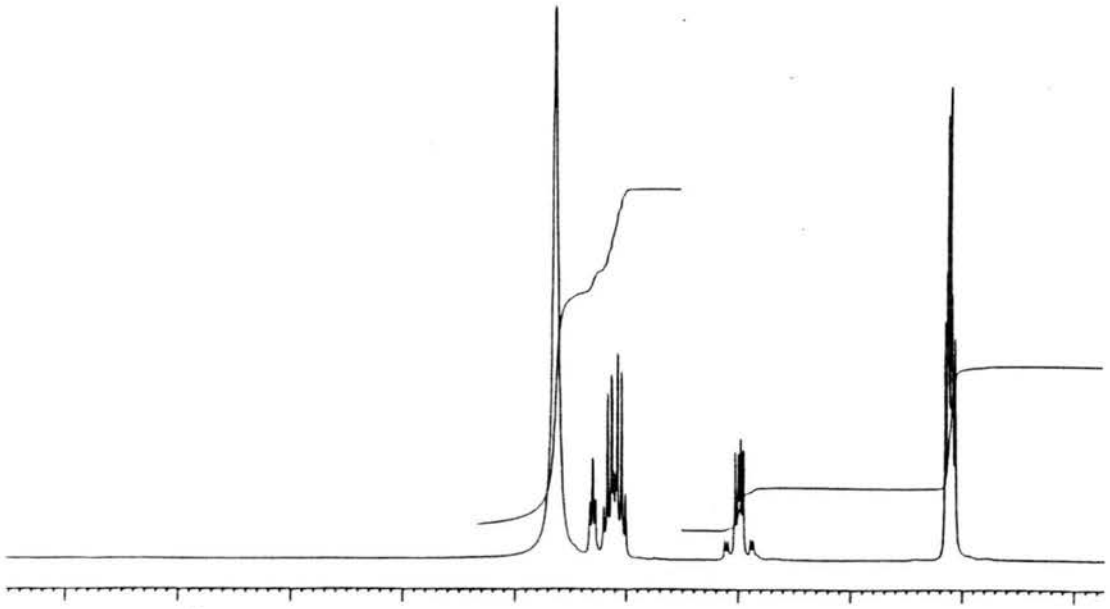


205 **205'**

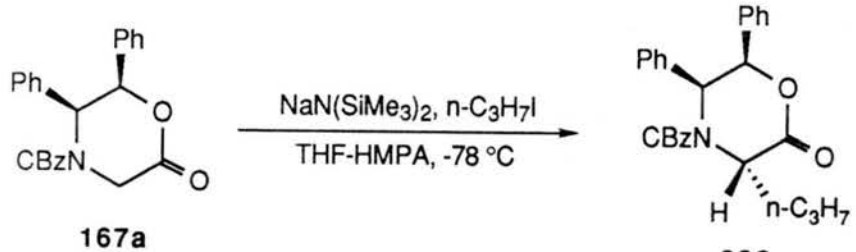
(R)-Diethyl Aspartate Hydrochloride (205')

205 was dissolved in 1N HCl•EtOH. The resulting solution was brought to reflux. After 2 hr the solvent was evaporated off, and the residue was triturated with Et_2O to yield **205'** as white solid.

^{1}H NMR (200 MHz, D_2O, vs HOD) d 1.08-1.15 (6H, m), 2.93 (1H, dd, J = 16.89 Hz, J = 4.83 Hz), 3.07 (1H, dd, J = 17.81 Hz, J = 5.82 Hz), 4.05 (2H, q, J = 7.16 Hz), 4.14 (2H, q, J =7.17 Hz), 4.31 (1H, t, J = 5.82 Hz); $[\alpha]^{25}_D$ -7.4° (c 0.7, H_2O), Lit.[49b] -7.4° (c 1, H_2O).



^{1}H NMR of **205'** in D_2O at 295 °K

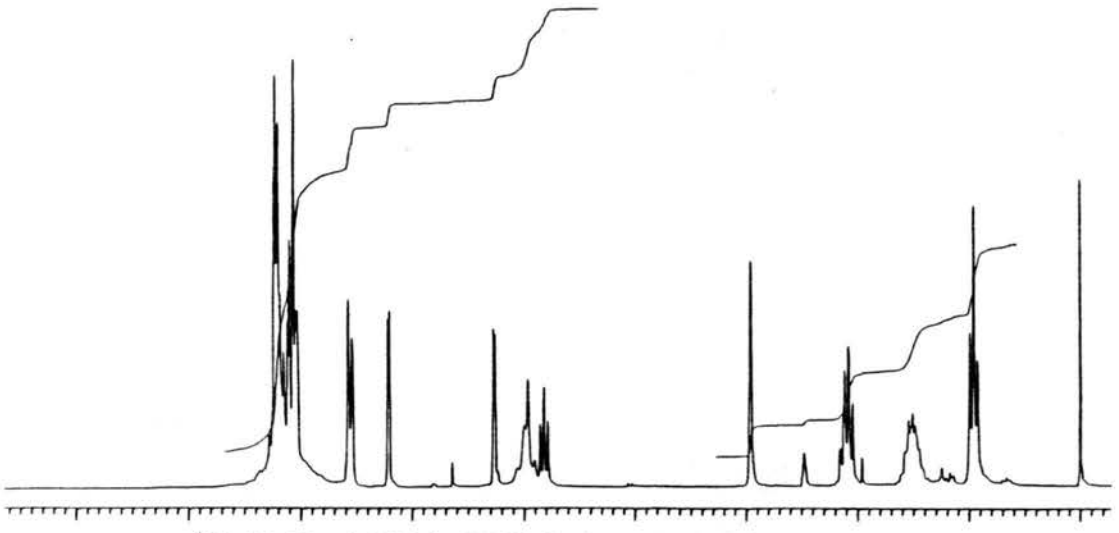


167a **206**

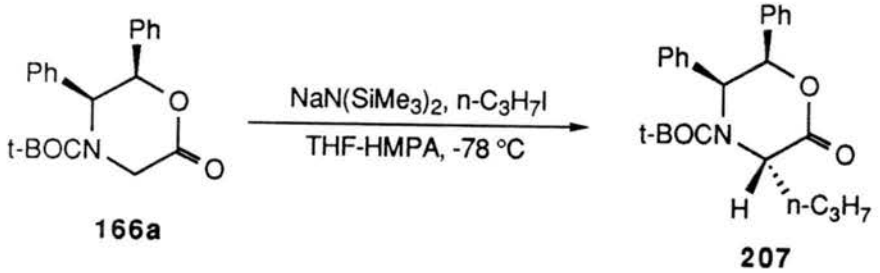
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (206)

To a stirred solution of **167a** (300 mg, 0.774 mmol, 1 equiv) and n-propyl iodide (755 µl, 7.74 mmol, 10 equiv) in THF (16 ml) and HMPA (1.6 ml) was added sodium bis(trimethylsilyl)amide (1.16 ml, 1.16 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 40 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 253mg (76.1%) of **206** as white solid and 8 mg (2.7%) of unreacted **167a**.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.96 (3H, t, J = 7.24 Hz), 1.40-1.62 (2H, m), 2.03-2.18 (2H, m), 4.82 (1H, t, J = 7.22 Hz), 4.93 (1H, 1/2ABq, J = 12.40 Hz), 5.03 (1H, 1/2ABq, J = 12.40 Hz), 5.26 (1H, d, J = 3.06 Hz), 6.21 (1H, d, J = 3.07 Hz), 6.56 (2H, d, J = 6.96 Hz), 7.02-7.28 (13H, m); IR (NaCl, CH_2Cl_2) 1754, 1702 cm^{-1}; mp 141-142 °C; $[\alpha]^{25}_D$ -50.1° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.56; H, 6.27; N, 3.38.



^{1}H NMR of **206** in DMSO-d_6 at 393 °K



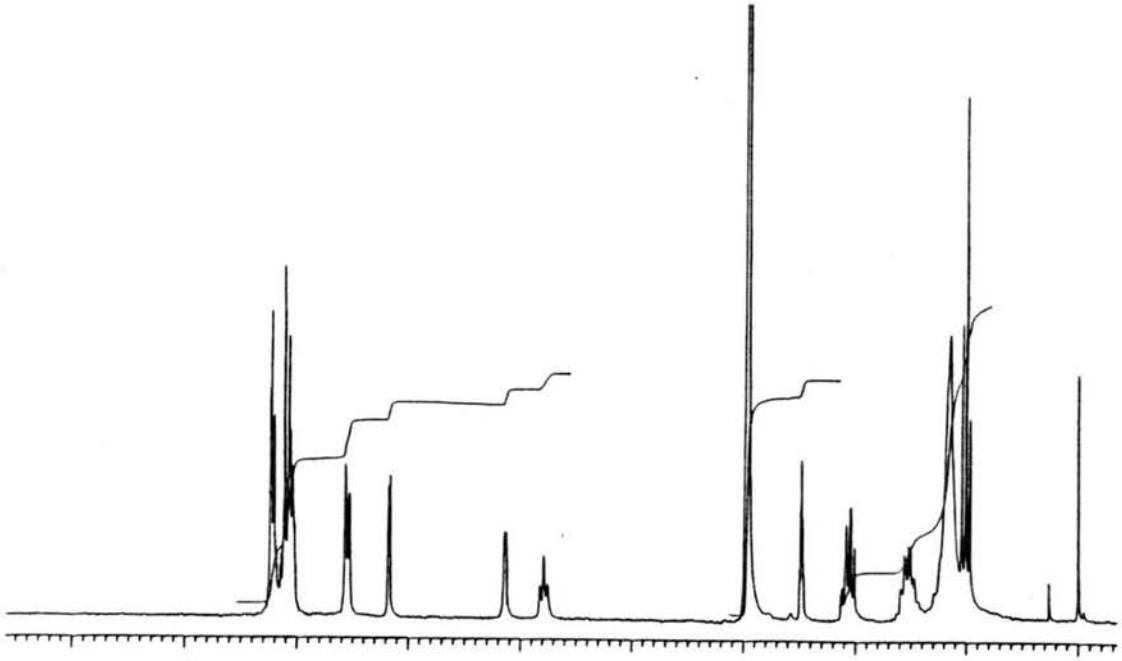
166a **207**

(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (207)

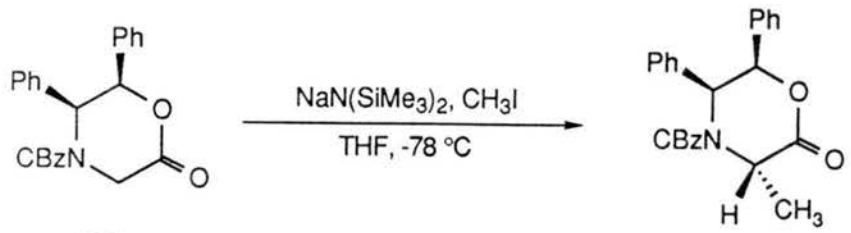
To a stirred solution of **166a** (500 mg, 1.416 mmol, 1 equiv) and n-propyl iodide (1.38 ml, 14.15 mmol, 10 equiv) in THF (7 ml) and HMPA (0.7 ml)

was added sodium bis(trimethylsilyl)amide (2.12 ml, 2.12 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 40 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 429 mg (76.7%) of **207** as white solid and 76 mg (12.3%) of dialkylated lactone as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.00 (3H, t, J = 7.28 Hz), 1.12 (9H, s), 1.45-1.61 (2H, m), 2.09-2.14 (2H, m), 4.79 (1H, t, J =7.18 Hz), 5.14 (1H, d, J = 2.64 Hz), 6.17 (1H, d, J = 3.10 Hz), 6.53-6.59 (2H, m), 7.02-7.27 (8H, m); IR (NaCl, CH_2Cl_2) 1749, 1702 cm^{-1}; mp 182-183 °C; $[\alpha]^{25}_D$ -68.8° (c 0.56, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.68; H, 7.38; N, 3.59.



^{1}H NMR of **207** in DMSO-d_6 at 393 °K

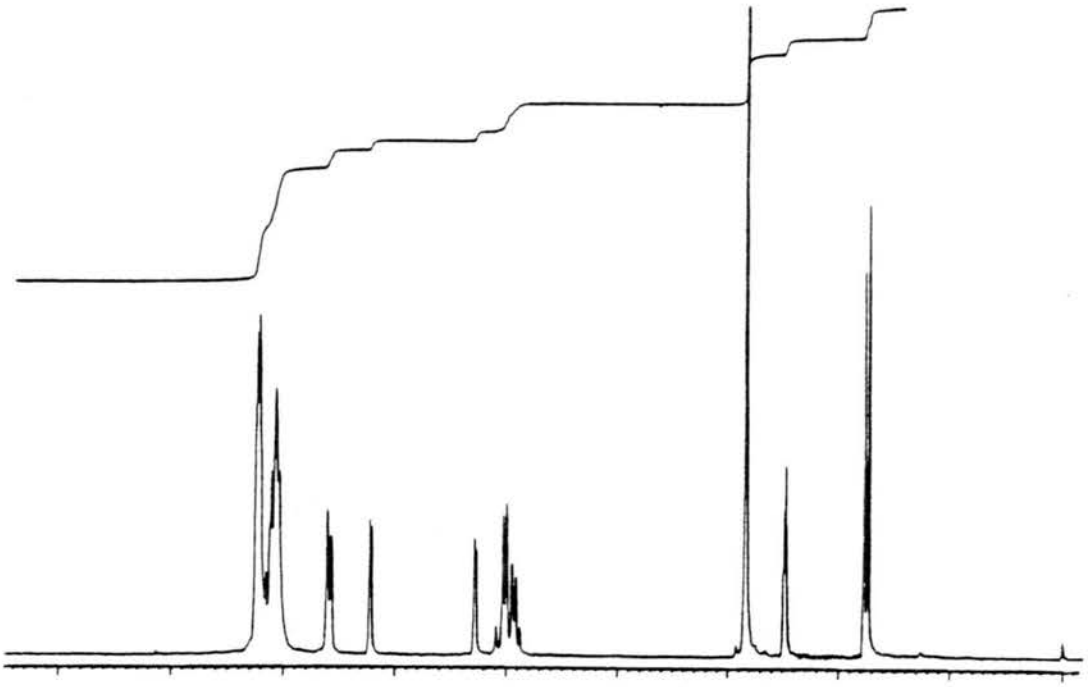


167a 208

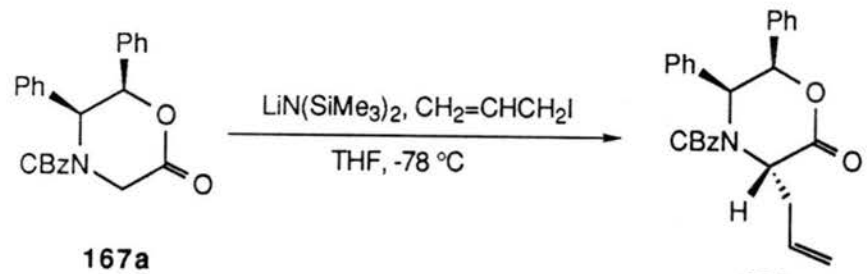
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (208)

To a stirred solution of **167a** (2 g, 5.162 mmol, 1 equiv) and methyl iodide (3.21 ml, 51.56 mmol, 10 equiv) in THF (90 ml) was added sodium bis(trimethylsilyl)amide (7.74 ml, 7.74 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 1.83 g (88%) of **208** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.74 (3H, d, J = 7.02 Hz), 4.92 (1H, q, J = 7.21 Hz), 4.95 (1H, 1/2ABq, J = 12.78 Hz), 5.08 (1H, 1/2ABq, J = 12.69 Hz), 5.27 (1H, d, J = 2.98 Hz), 6.23 (1H, d, J = 3.03 Hz), 6.57 (2H, d, J = 3.03 Hz), 7.03-7.28 (13H, m); IR (NaCl, CH_2Cl_2) 1757, 1702 cm^{-1}; mp 186-187 °C, Lit.[49b] 186-187 °C; $[\alpha]^{25}_D$ -49.8° (c 1, CH_2Cl_2), Lit.[49b] -50° (c 1.04, CH_2Cl_2).



^{1}H NMR of **208** in DMSO-d_6 at 393 °K



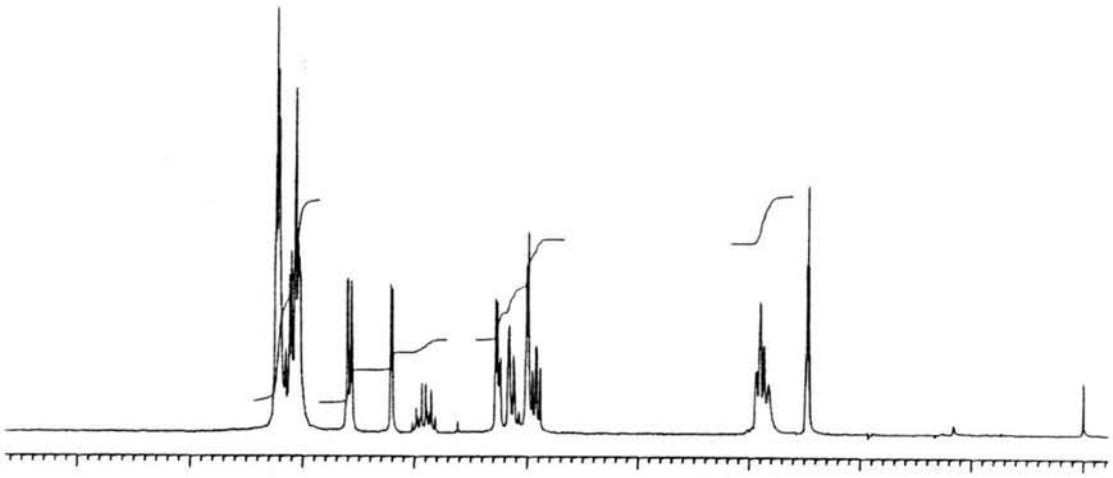
167a **209**

(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2'-propenyl) -2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (209)

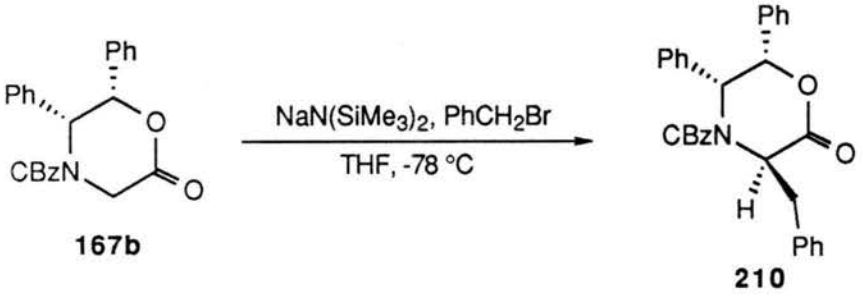
To a stirred solution of **167a** (1.5 g, 3.872 mmol, 1 equiv) and allyl iodide (1.77 ml, 19.36 mmol, 5 equiv) in THF (130 ml) was added lithium bis(trimethylsilyl)amide (4.65 ml, 4.65 mmol, 1.2 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 2 hr the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by

column chromatography on silica gel to afford 1.35 g (81.6%) of **209** as white solid .

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) d 2.82-2.96 (2H, m), 4,92 (1H, t, J = 6.94 Hz), 4.95 (1H, 1/2ABq, J = 12.63 Hz), 5.04 (1H, 1/2ABq, J = 12.76 Hz), 5.11-5.25 (2H, m), 5.27 (1H, d, J = 3.11 Hz), 5.82-6.02 (1H, m), 6.20 (1H, d, J = 3.08 Hz), 6.56-6.61 (2H, m), 7.02-7.24 (13H, m); IR (NaCl, CH_2Cl_2) 1757, 1705 cm^{-1}; mp 166-168 °C, Lit.[49b] 165 °C; $[\alpha]^{25}_D$ -29.3° (c 1, CH_2Cl_2), Lit.[49b] -29.2° (c 1.05, CH_2Cl_2).



^{1}H NMR of **209** in DMSO-d_6 at 393 °K



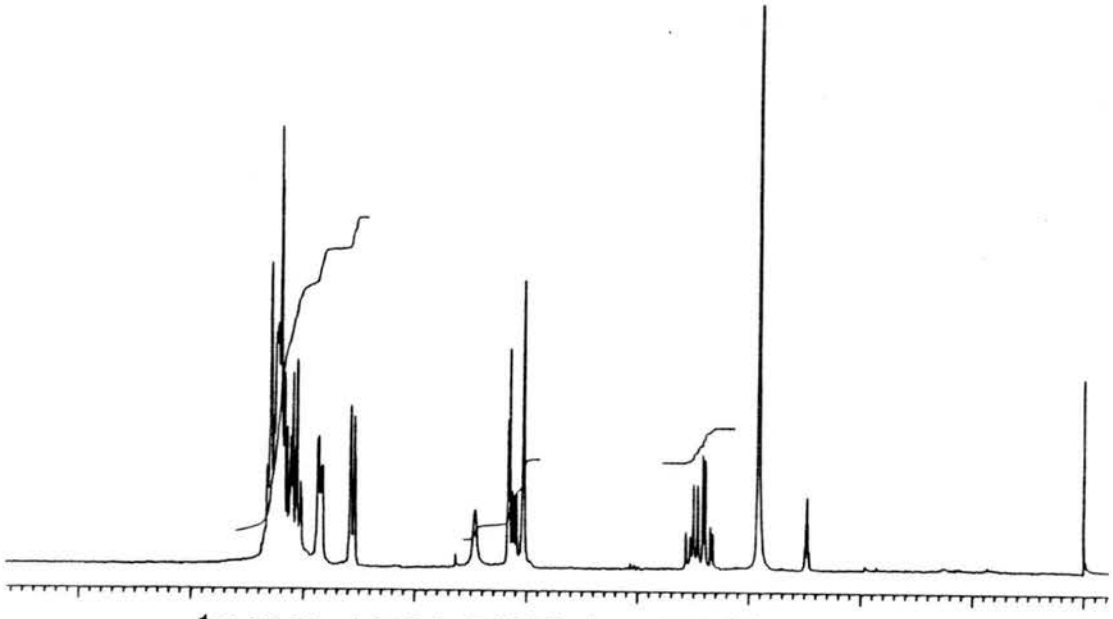
167b **210**

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-benzyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (210)

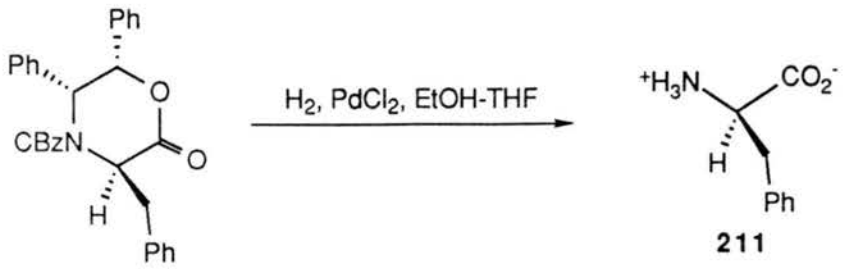
To a stirred solution of **167b** (300 mg, 0.774 mmol, 1 equiv) and benzyl bromide (276 µl, 2.32 mmol, 1.2 equiv) in THF (20 ml) was added sodium

bis(trimethylsilyl)amide (929 µl, 0.929 mmol, 1.2 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 40 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 286 mg (77.3%) of **210** as white solid and 29 mg (6.3%) of the dialkylated product as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 3.37 (1H, dd, J = 13.81 Hz, J = 4.31 Hz), 3.51 (1H, dd, J = 13.74 Hz, J = 8.01 Hz), 5.03 (2H, s), 5.12 (1H, dd, J = 8.08 Hz, J = 4.40 Hz), 5.16 (1H, d, J =3.22 Hz), 5.46 (1H, d, J = 1.24 Hz), 6.54-6.58 (2H, m), 6.82-6.88 (2H, m), 6.99-7.35 (16H, m); IR (NaCl, CH_2Cl_2) 1753, 1706 cm^{-1}; mp 183-184 °C; $[\alpha]^{25}_D$ -62.8° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{31}H_{27}NO_4$: C, 77.96; H, 5.70; N, 2.93. Found: C, 78.12; H, 5.70; N, 2.95.



^{1}H NMR of **210** in DMSO-d_6 at 393 °K

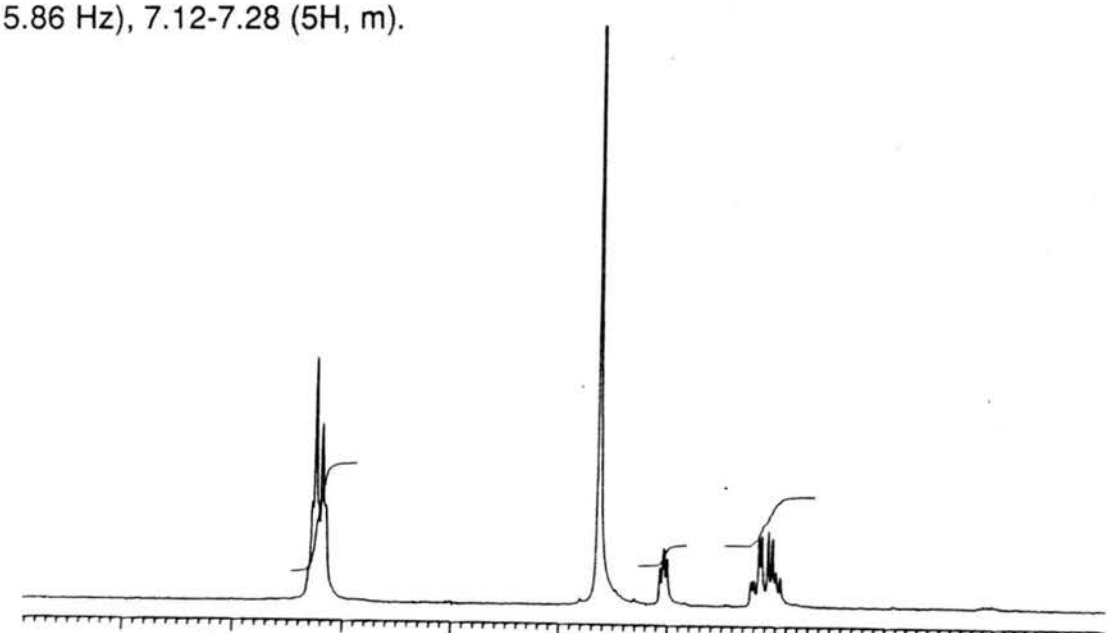


210 **211**

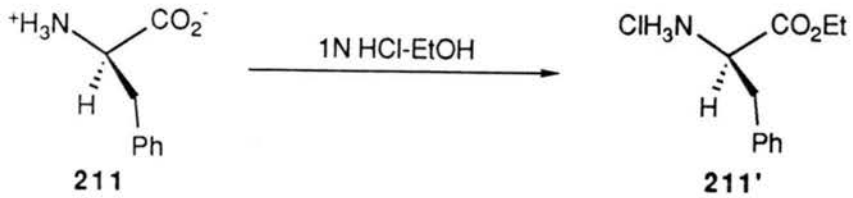
(R)-Phenylalanine (211)

To a solution of **210** (140 mg, 0.293 mmol, 1 equiv) in THF and EtOH (1.5 ml, 1:2) was added palladium chloride (15.6 mg, 0.088 mmol, 0.3 equiv). The reaction mixture was hydrogenated at 50 psi for 20 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 52 mg (107%) of **211** as white solid. This material was used without further purification for the next step: >99% ee ; adjusted chemical yield 93%.

^1H NMR (200 MHz, D_2O, vs HOD) δ 3.01 (1H, dd, J = 14.53 Hz, J = 7.76 Hz), 3.18 (1H, dd, J = 14.47 Hz, J = 5.38 Hz), 4.03 (1H, dd, J = 7.27 Hz, J = 5.86 Hz), 7.12-7.28 (5H, m).



^1H NMR of **211** in D_2O at 295 °K

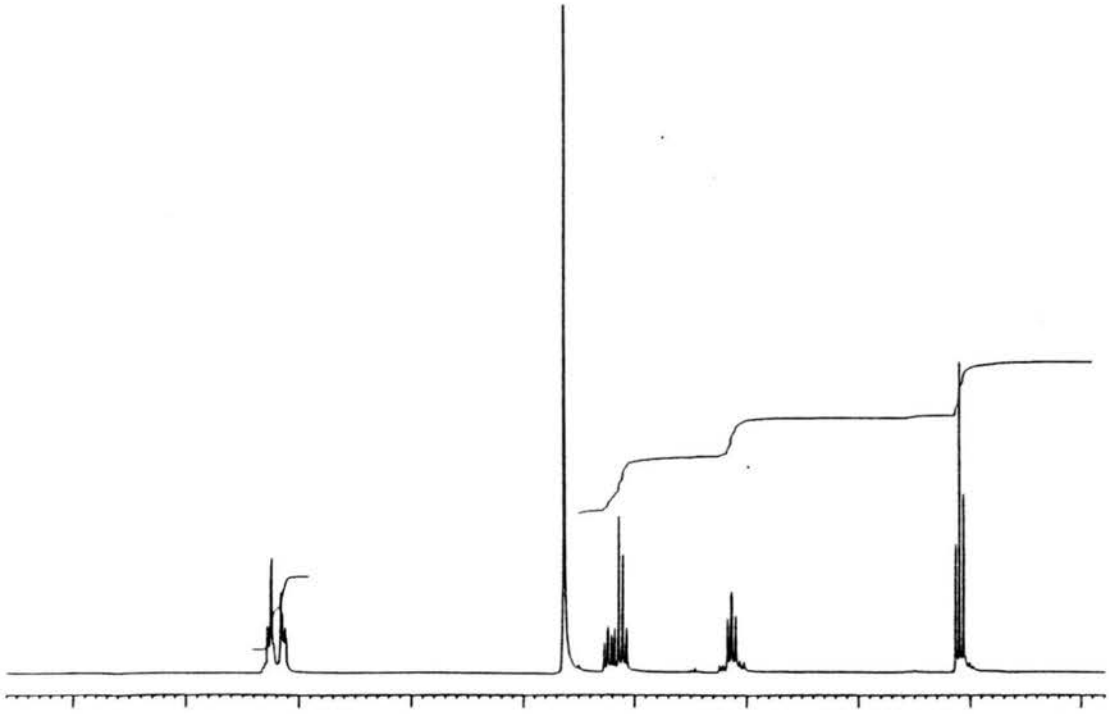


211 211'

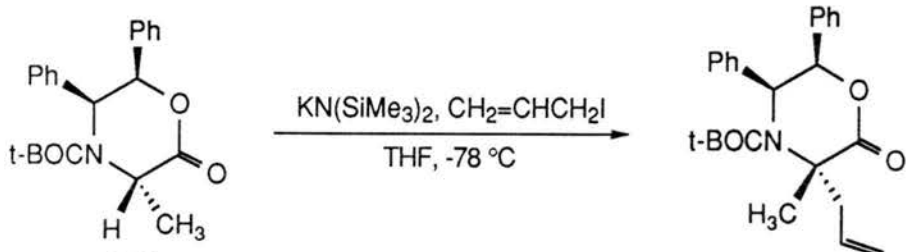
(R)-Phenylalanine Ethylester Hydrochloride (211')

211 was dissolved in 1N HCl•EtOH. The resulting solution was brought to reflux. After 2 hr the solvent was evaporated off, and the residue was triturated with Et_2O to yield **211'** as white solid.

^1H NMR (270 MHz, D_2O, vs HOD) d 1.09 (3H, t, J = 6.85 Hz), 3.08 (1H, dd, J = 17.02 Hz, J = 7.63 Hz), 3.19 (1H, dd, J = 16.26 Hz, J = 6.94 Hz), 4.12 (2H, q, J = 7.19 Hz), 4.23 (1H, dd, J =7.26 Hz, J = 6.18 Hz), 7.08-7.29 (5H, m); IR (ZnS, MeOH) 2934, 1743 cm^{-1}; mp 153-154 °C, Lit.[77] (L) Phenylalanine ethyl ester•HCl 155-156 °C; $[\alpha]^{25}_D$ -32.3° (c 0.7, EtOH), Lit.[77] (L) Phenylalanine ethyl ester•HCl +33.2° (c 5, EtOH).



^1H NMR of **211'** in D_2O at 295 °K

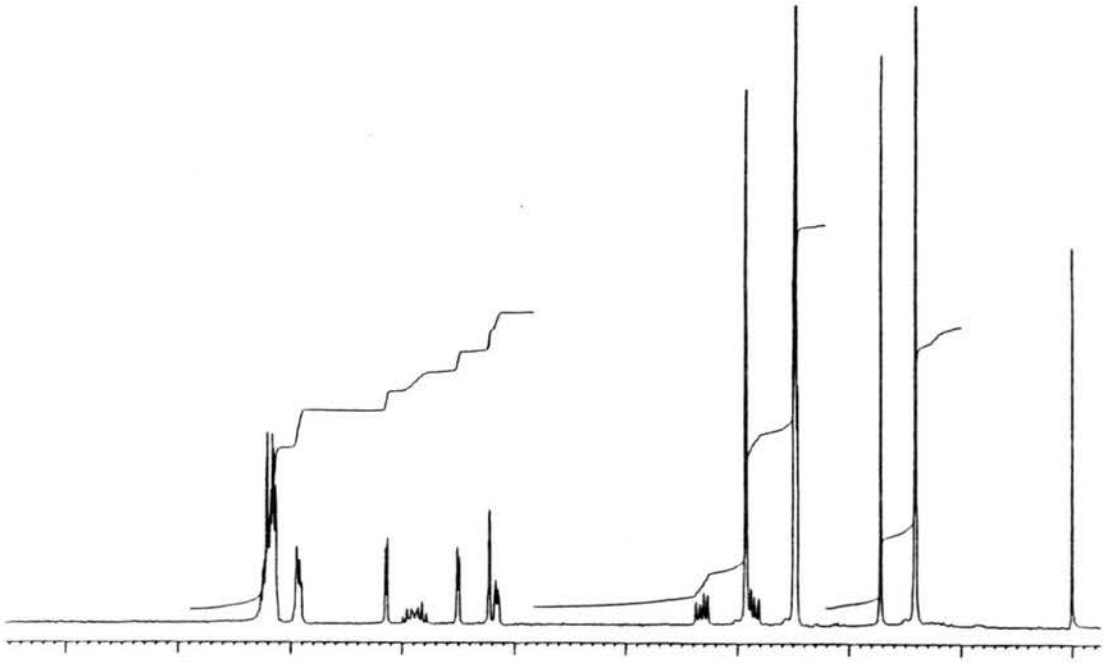


192 213

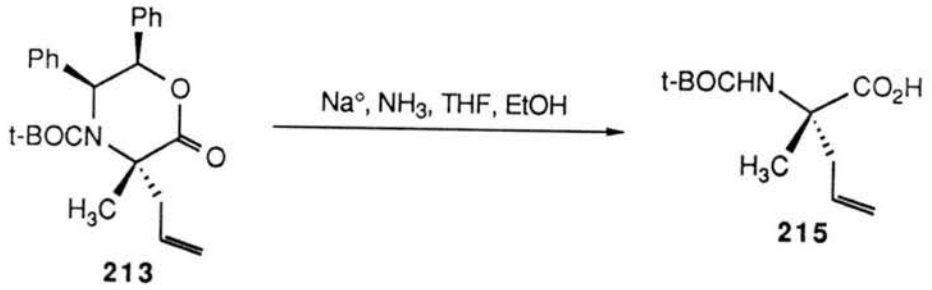
(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(2'-propenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (213)

To a stirred solution of **192** (500 mg, 1.361 mmol, 1 equiv) and allyl iodide (373 µl, 4.079 mmol, 3 equiv) in THF (6 ml) was added potassium bis(trimethylsilyl)amide (1.94 ml, 2.72 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 481 mg (86.7%) of **213** as white oily solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.41 (9H, s), 1.72 (3H, s), 2.86 (1H, dd, J = 13.92 Hz, J = 7.83 Hz), 3.32 (1H, dd, J = 13.94 Hz, J = 7.31 Hz), 5.14-5.22 (2H, m), 5.50 (1H, d, J = 3.23 Hz), 5.78-5.99 (1H, m), 6.14 (1H, d, J = 3.32 Hz), 6.89-6.95 (2H, m), 7.13-7.25 (8H, m); IR (NaCl, CH_2Cl_2) 1746, 1700 cm^{-1}; mp 83-84 °C; $[\alpha]^{25}_D$ +46.5° (c 1, CH_2Cl_2). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.55; H, 7.07; N, 3.45.



^{1}H NMR of **213** in DMSO-d_6 at 393 °K

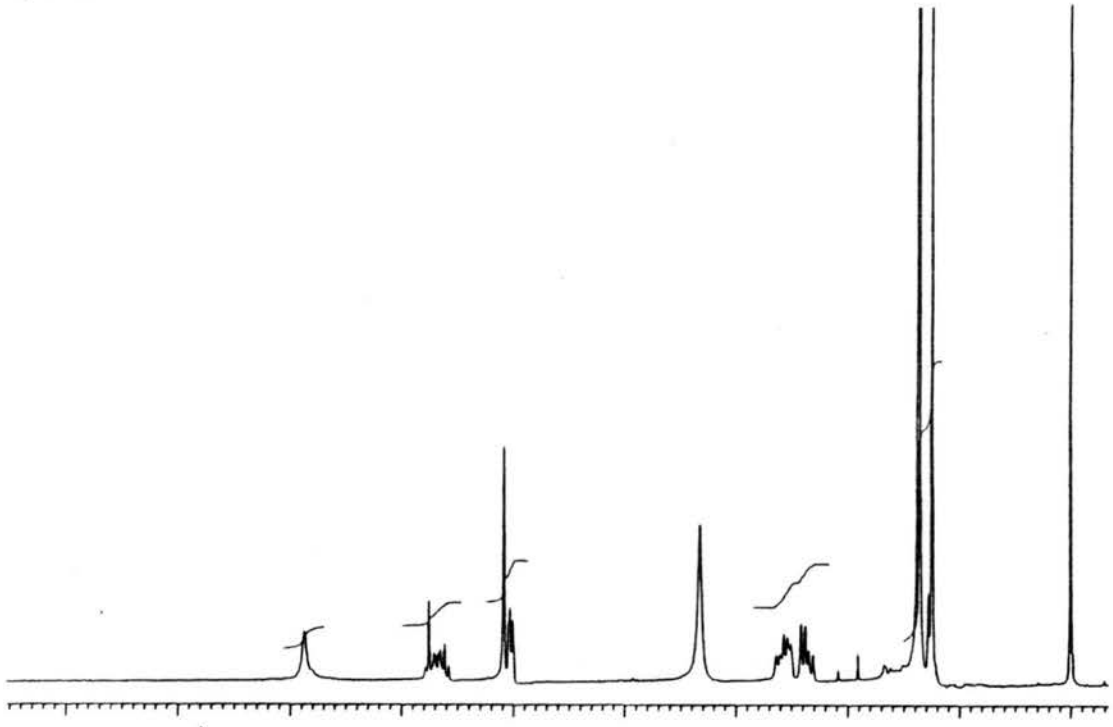


(S)-N-(tert-Butyloxycarbonyl)-2-(2'-propenyl)alanine (215)

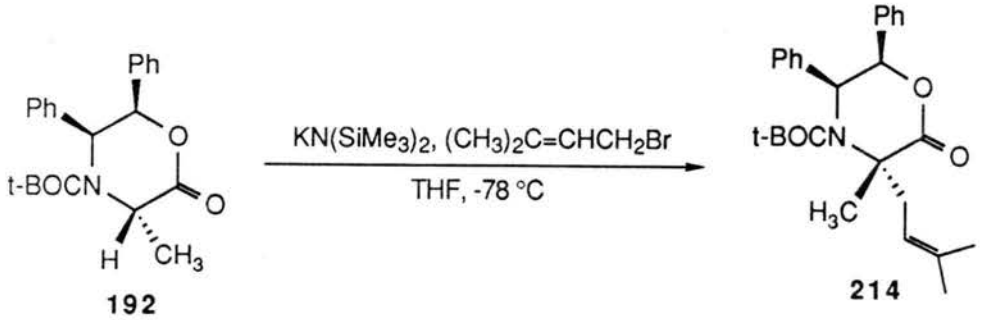
To a solution of Na° (169 mg, 7.35 mmol, 15 equiv) in liquid ammonia (50 ml, distilled from Na°) was added a solution of **213** (200 mg, 0.49 mmol, 1 equiv) and ethanol (300 µl) in THF (5 ml) via syringe at -33 °C. After 30 min the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm to ambient temperature. The ammonia was allowed to evaporate off, and the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 2 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated

and separated by PTLC on silica gel to afford 79 mg (70%) of **215** as colorless oil: 100 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.25 (3H, s), 1.37 (9H, s), 2.36 (1H, dd, J = 13.73 Hz, J = 7.64 Hz), 2.59 (1H, dd, J = 13.56 Hz, J= 7.11 Hz), 4.99-5.11 (2H, m), 5.59-5.80 (1H, m), 6.88 (1H, br. s, D_2O exch.); IR (NaCl, $CDCl_3$) 1715, 1694, 1651, 1500 cm^{-1}; $[\alpha]^{25}_D$ -13.6° (c 1.1, CH_2Cl_2). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.36; N, 6.11. Found: C, 57.88; H, 8.29; N, 6.06.



^{1}H NMR of **215** in DMSO-d_6 at 295 °K

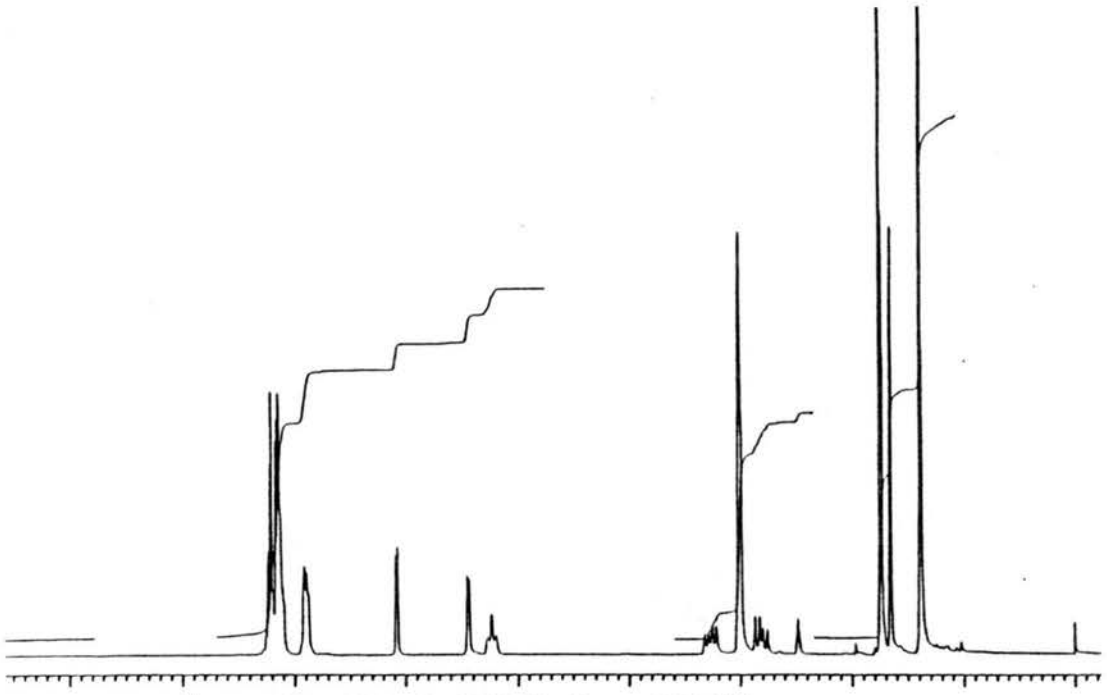


192 214

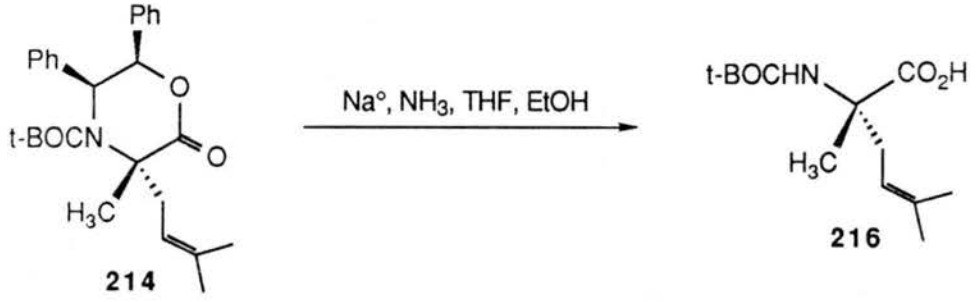
(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(3'-methyl-2'-butenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (214)

To a stirred solution of **192** (500 mg, 1.361 mmol, 1 equiv) and 1-bromo-3-methyl-2-butene (791 µl, 6.804 mmol, 5 equiv) in THF (6 ml) was added potassium bis(trimethylsilyl)amide (1.94 ml, 2.72 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 475 mg (80.1%) of **214** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.39 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 1.75 (3H, s), 2.81 (1H, dd, J = 14.36 Hz, J = 8.32 Hz), 3.27 (1H, dd, J = 14.29 Hz, J = 7.50 Hz), 5.24 (1H, t, J = 7.99 Hz), 5.44 (1H, d, J = 3.17 Hz), 6.08 (1H, d, J = 3.24 Hz), 6.87-6.92 (2H, m), 7.10-7.25 (8H, m); IR (NaCl, CH_2Cl_2) 1746, 1702 cm^{-1}; mp 139-140 °C; $[\alpha]^{25}_D$ +55.1° (c 0.9, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.52; H, 7.78; N, 3.40.



^{1}H NMR of **214** in DMSO-d_6 at 393 °K



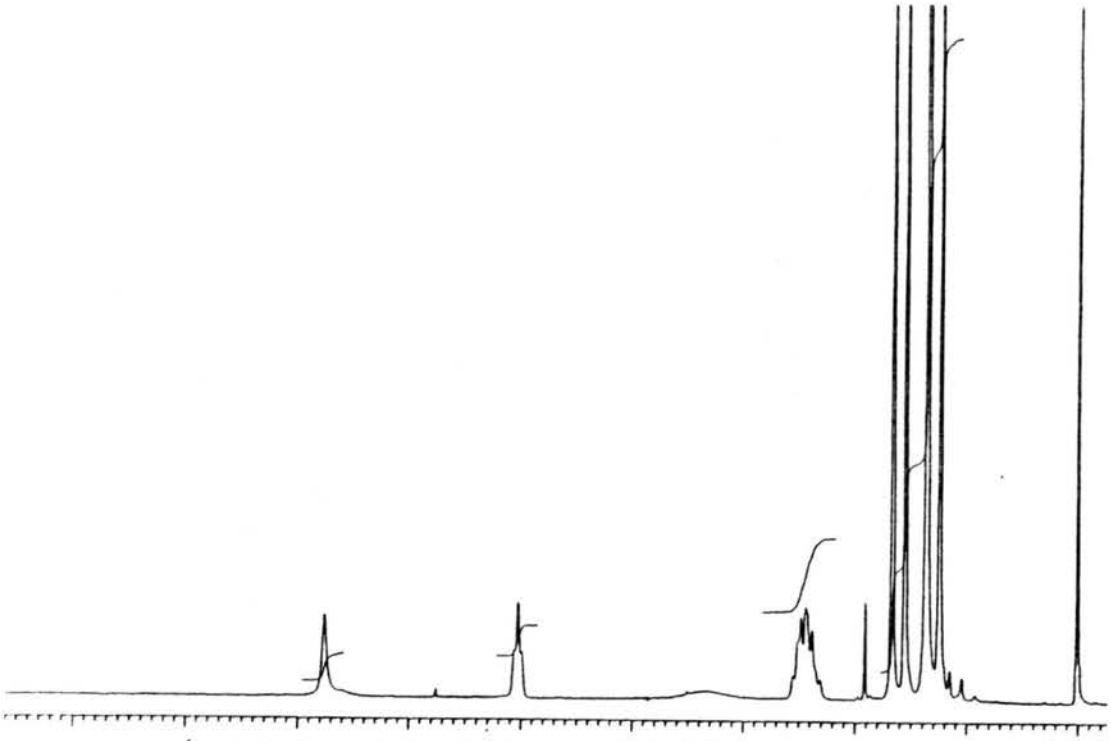
214 **216**

(S)-N-(tert-Butyloxycarbonyl)-2-(3'-methyl-2'-butenyl)alanine(216)

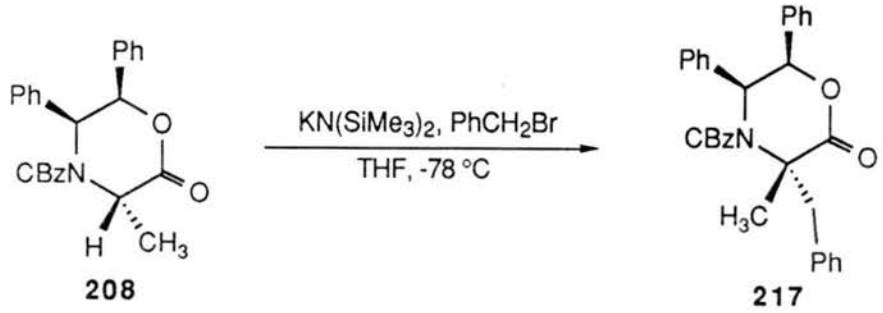
To a solution of Na° (69 mg, 3.001 mmol, 13 equiv) in liquid ammonia (25 ml, distilled from Na°) was added a solution of **214** (100 mg, 0.230 mmol, 1 equiv) and ethanol (200 µl) in THF (3 ml) via syringe at -33 °C. After 10 min the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm to ambient temperature. The ammonia was allowed to evaporate off, and the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 2 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate,

filtered, concentrated and separated by PTLC on silica gel to afford 38.4 mg (65%) of **216** as colorless oil: 100 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.24 (3H, s), 1.35 (9H, s), 1.56 (3H, s), 1.67 (3H, s), 2.30-2.57 (2H, m), 5.03 (1H, t, J = 7.06 Hz), 6.76 (1H, br. s, D_2O exch.); IR (NaCl, $CDCl_3$) 1715, 1653, 1498 cm^{-1}; $[\alpha]^{25}_D$ -13.4° (c 0.87, CH_2Cl_2). Anal. Calcd for $C_{28}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.60; H, 9.06; N, 5.48.



^{1}H NMR of **216** in DMSO-d_6 at 295 °K

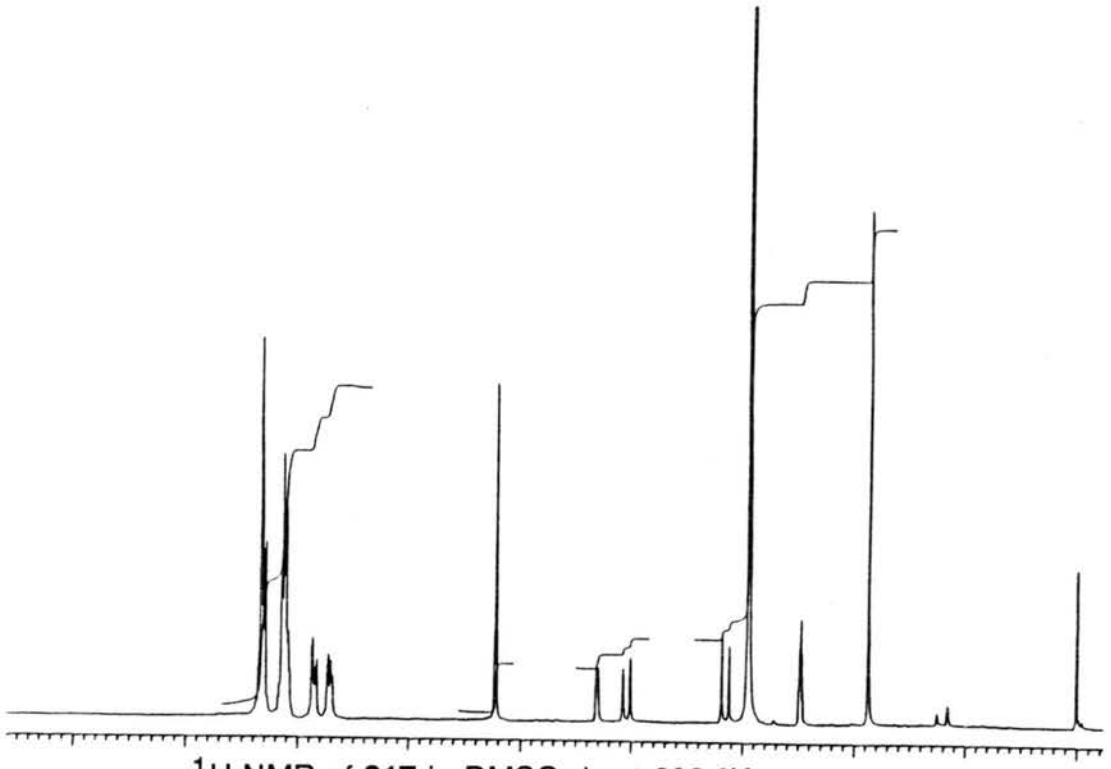


208 217

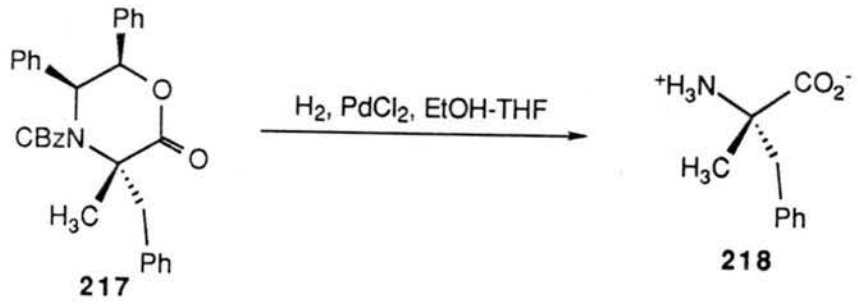
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-benzyl-3-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (217)

To a stirred solution of **208** (500 mg, 1.245 mmol, 1 equiv) and benzyl bromide (740 μl, 6.221 mmol, 5 equiv) in THF (12 ml) was added potassium bis(trimethylsilyl)amide (1.80 ml, 2.49 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 514 mg (84%) of **217** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.95 (3H, s), 3.16 (1H, 1/2 ABq, J = 13.44 Hz), 4.05 (1H, 1/2 ABq, J = 13.23 Hz), 4.30 (1H, d, J = 3.31 Hz), 5.22 (2H, s), 5.22 (1H, d, J = 3.29 Hz), 6.68-6.74 (2H, m), 6.82-6.88 (2H, m), 7.09-7.15 (8H, m), 7.29-7.34 (8H, m); IR (NaCl, CH_2Cl_2) 1745, 1703 cm^{-1}; mp 134-135 °C; $[\alpha]^{25}_D$ +165.4° (c 0.8, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.34; H, 6.03; N, 2.88.



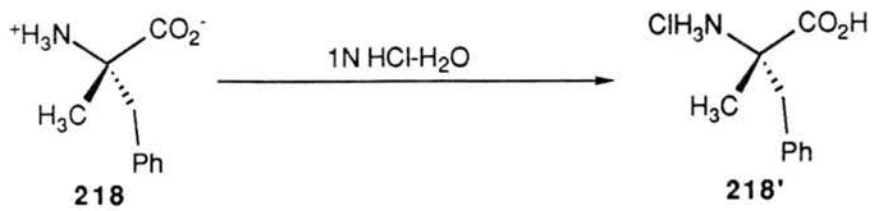
^{1}H NMR of **217** in DMSO-d_6 at 393 °K



217 **218**

(S)-2-Methylphenylalanine (218)

To a solution of **217** (100 mg, 0.203 mmol, 1 equiv) in THF and EtOH (3 ml, 1:1) was added palladium chloride (18 mg, 0.102 mmol, 0.5 equiv). The reaction mixture was hydrogenated at 50 psi for 48 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 39.2 mg (108%) of **218** as white solid. This material was converted into the hydrochloride salt directly without further purification: 100 % ee; adjusted chemical yield 93%.

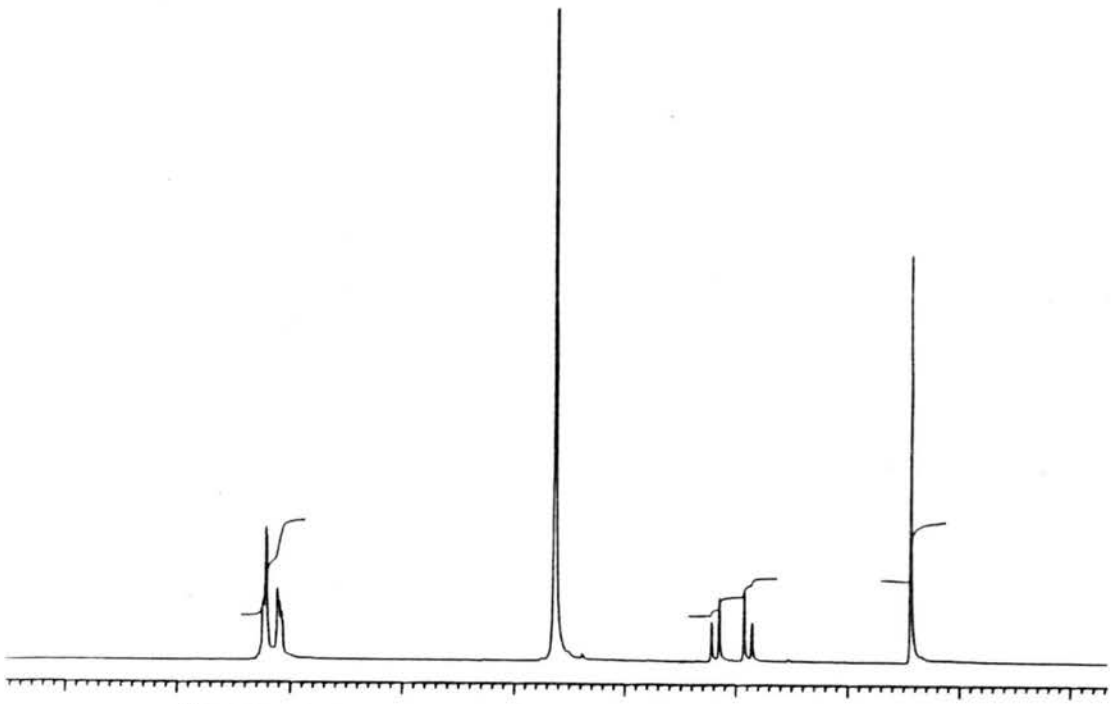


218 **218'**

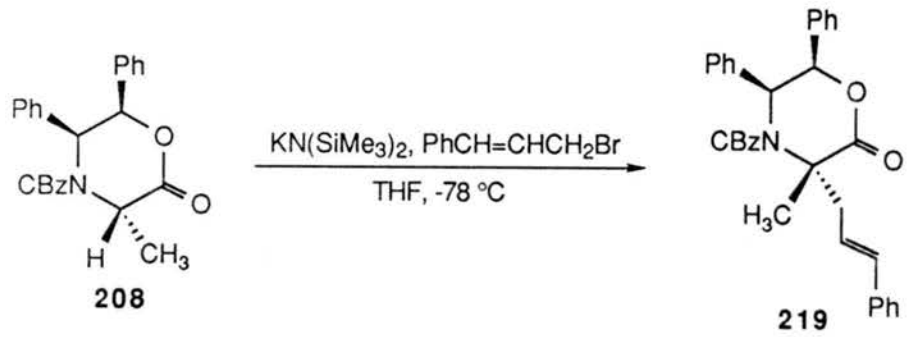
(S)-2-Methylphenylalanine Hydrochloride (218')

218 was dissolved in 1N HCl•H_2O. The resulting solution was brought to reflux. After 2 hr the solvent was evaporated off, and the residue was triturated with Et_2O to yield **218'** as white solid.

^1H NMR (200 MHz, D_2O, vs HOD) δ 1.44 (3H, s), 2.89 (1H, 1/2 ABq, J = 14.33 Hz), 3.18 (1H, 1/2 ABq, J = 14.30 Hz), 7.08-7.11 (2H, m), 7.21-7.26 (3H, m); IR (ZnS, MeOH) 3406, 2925, 1733 cm^{-1}; mp 203-205 °C (decom.); $[\alpha]^{25}D$ -9.6° (c 0.2, H_2O). Anal. (recrystallized from EtOH/Et_2O) Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.48; H, 6.49; N, 6.29.



^1H NMR of **218'** in D_2O at 295 °K

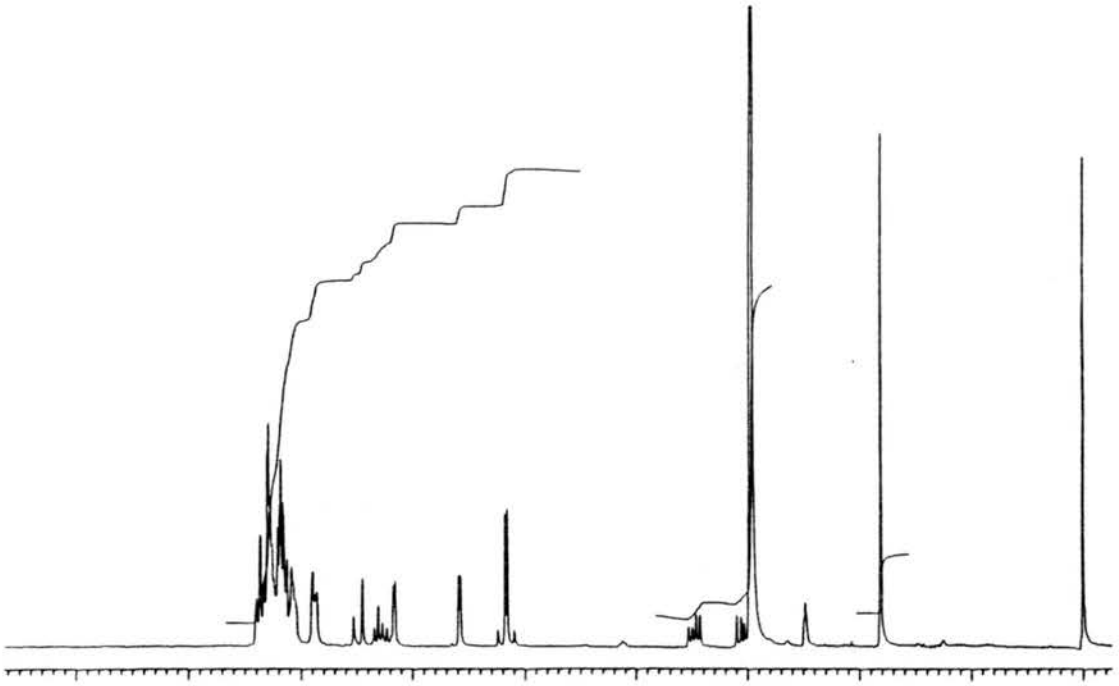


208 219

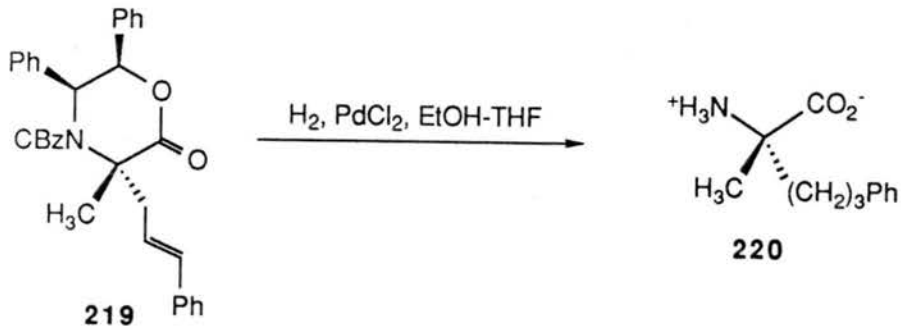
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(3'-phenyl-2'-propenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (219)

To a stirred solution of **208** (354 mg, 0.882 mmol, 1 equiv) and cinnamyl bromide (869 mg, 4.409 mmol, 5 equiv) in THF (12 ml) was added potassium bis(trimethylsilyl)amide (1.26 ml, 1.764 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 366 mg (80.2%) of **219** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.81 (3H, s), 3.04 (1H, dd, J = 13.76 Hz, J = 7.84 Hz), 3.48 (1H, dd, J = 13.88 Hz, J = 6.75 Hz), 5.13 (1H, 1/2 ABq, J = 12.51 Hz), 5.21 (1H, 1/2 ABq, J = 12.60 Hz), 5.58 (1H, d, J = 3.17 Hz), 6.16 (1H, d, J = 3.20 Hz), 6.20-6.35 (1H, m), 6.47-6.54 (1H, m), 6.85-6.92 (2H, m), 7.05-7.41 (18H, m); IR (NaCl, CH_2Cl_2) 1746, 1705 cm^{-1}; mp 162-163 °C; $[\alpha]^{25}_D$ +127.8° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 78.93; H, 6.15; N, 2.76.



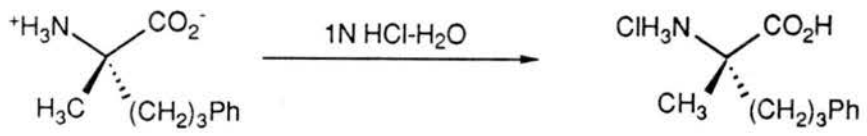
^{1}H NMR of **219** in DMSO-d_6 at 393 °K



219 **220**

(S)-2-(3'-Phenylpropyl)alanine (220)

To a solution of **219** (100 mg, 0.193 mmol, 1 equiv) in THF and EtOH (4 ml, 1:1) was added palladium chloride (24 mg, 0.135 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 50 psi for 37 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 43.3 mg (108%) of **220** as white solid. This material was converted into the hydrochloride salt directly without further purification: 100% ee; adjusted chemical yield 95%.

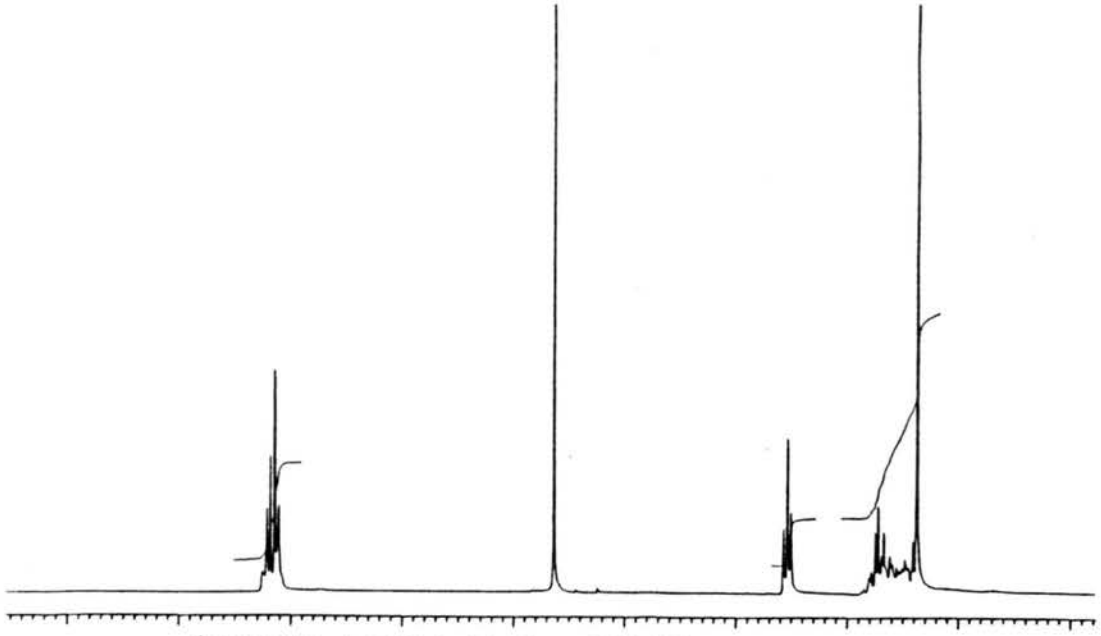


220 **220'**

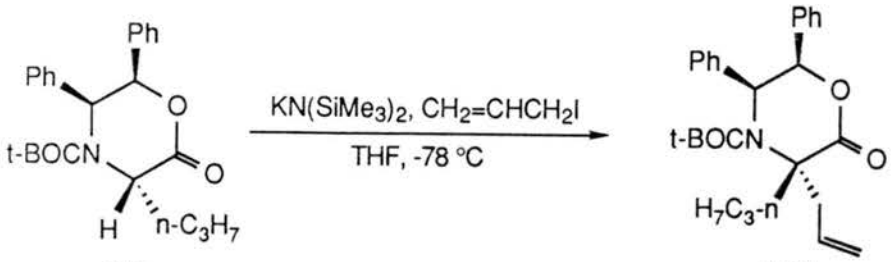
(S)-2-(3'-phenylpropyl)alanine Hydrochloride (220')

220 was dissolved in 1N HCl•H_2O. The resulting solution was brought to reflux. After 2 hr the solvent was evaporated off, and the residue was triturated with Et_2O to yield **220'** as white solid.

^1H NMR (200 MHz, D_2O, vs HOD) δ 1.37 (3H, s), 1.40-1.82 (4H, m), 2.53 (2H, t, J = 7.19 Hz), 7.10-7.28 (5H, m); IR (ZnS, MeOH) 2944, 1738, 1594, 1499 cm^{-1}; mp 246-248 °C (decom.); $[\alpha]^{25}_D$ +8.1° (c 0.2, H_2O). Anal. (recrystallized from i-PrOH/Et_2O) Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.44; N, 5.75. Found: C, 59.00; H, 7.57; N, 5.67.



^1H NMR of **220'** in D_2O at 295 °K

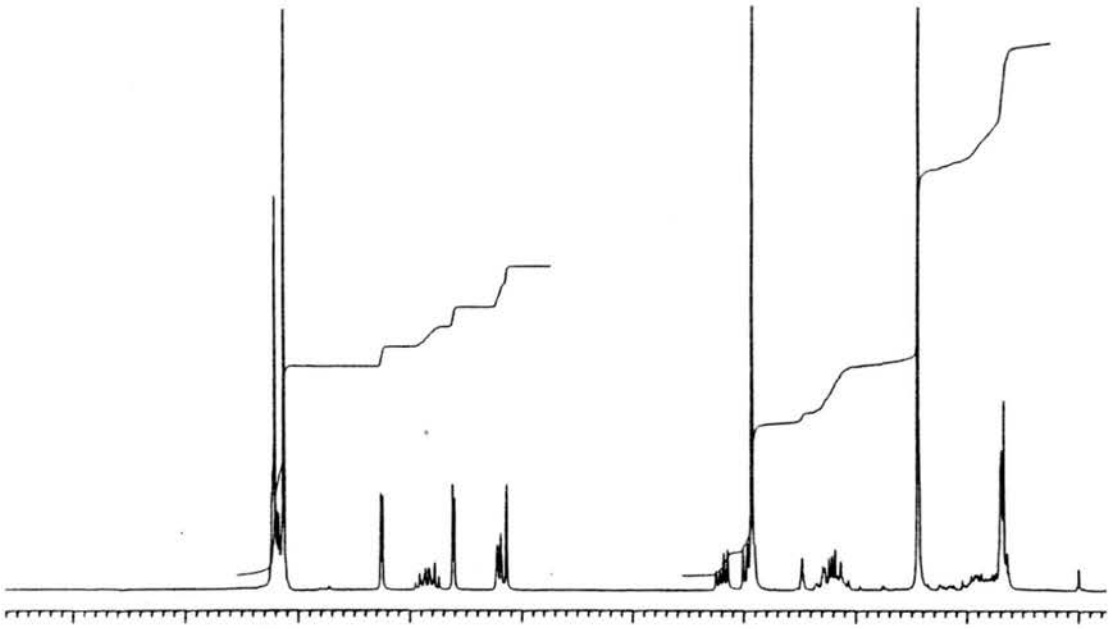


207 221

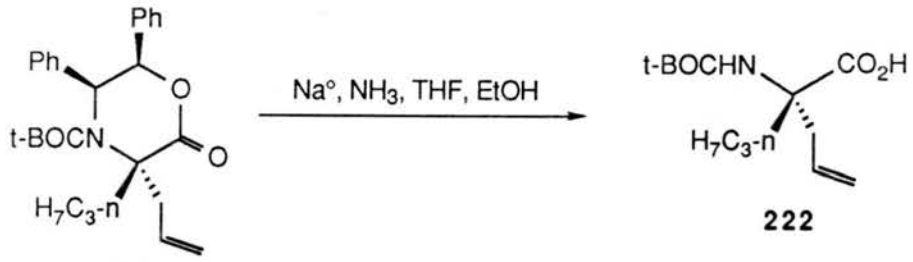
(3S,5S,6R)-4-(tert-Butyloxycarbonyl)-5,6-diphenyl-3-(2'-propenyl) -3-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (221)

To a stirred solution of **207** (500 mg, 1.264 mmol, 1 equiv) and allyl iodide (578 µl, 6.321 mmol, 5 equiv) in THF (6 ml) was added potassium bis(trimethylsilyl)amide (1.81 ml, 2.53 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by column chromatography on silica gel to afford 496 mg (90.1%) of **221** as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.68 (3H, t), 0.71-1.28 (2H, m), 1.43 (9H, s), 2.06-2.34 (2H, m), 2.92 (1H, dd, J = 14.08 Hz, J = 7.33 Hz), 3.19 (1H, dd, J = 13.92 Hz, J = 7.41 Hz), 5.12-5.22 (2H, m), 5.60 (1H, d, J = 3.24 Hz), 6.26 (1H, d, J = 3.41 Hz), 7.13-7.22 (10H, m); IR (NaCl, CH_2Cl_2) 1746, 1697 cm^{-1}; $[\alpha]^{25}_D$ +54.9° (c 3.3, CH_2Cl_2). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.49; H, 7.60; N, 3.25.



^{1}H NMR of **221** in DMSO-d_6 at 393 °K

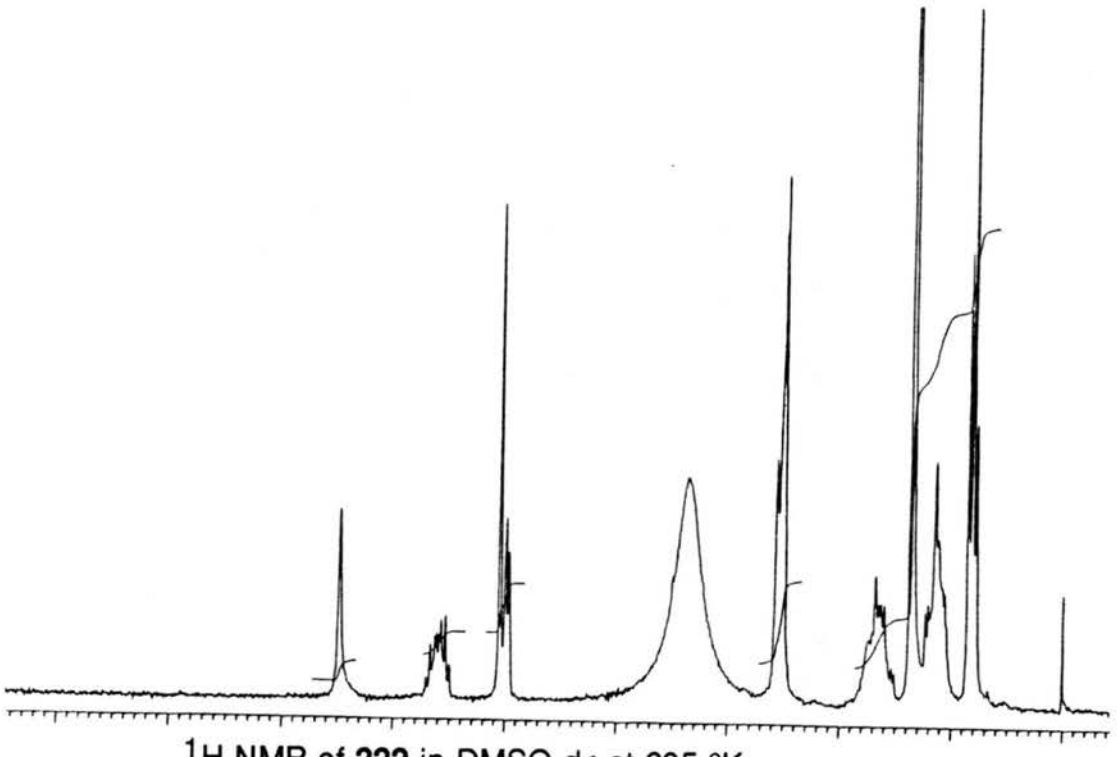


221 **222**

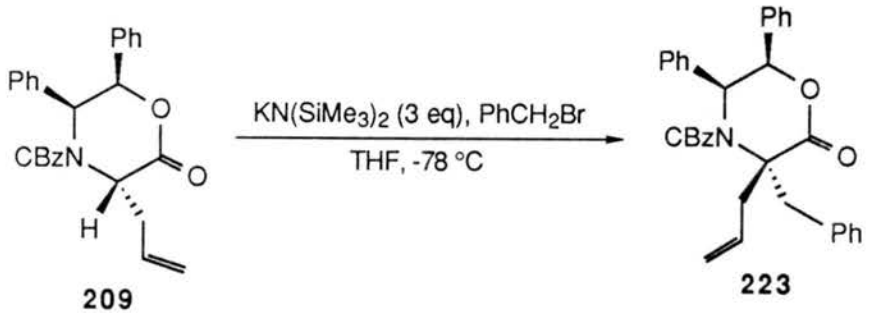
(S)-N-(tert-Butyloxycarbonyl)-2-(2'-propenyl)norvaline (222)

To a solution of Na° (69 mg, 3.001 mmol, 13 equiv) in liquid ammonia (25 ml, distilled from Na°) was added a solution of **221** (100 mg, 0.230 mmol, 1 equiv) and ethanol (200 µl) in THF (3 ml) via syringe at -33 °C. After 15 min the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted 2 × with ether and acidified to pH 2 with 1N HCl. After that the aqueous layer was extracted 3 × with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 35.4 mg (60%) of **222** as colorless oil: 100 % ee.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 0.82 (3H, t, J = 7.14 Hz), 1.07-1.22 (2H, m), 1.36 (9H, s), 1.52-1.81 (2H, m), 2.51-2.60 (2H, m), 4.98-5.06 (2H, m), 5.50-5.70 (1H, m), 6.49 (1H, s, D_2O exch.); IR (NaCl, $CDCl_3$) 1714, 1694, 1651, 1494 cm^{-1}; $[\alpha]^{25}_D$ -6.4° (c 0.45, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.08; H, 9.01; N, 5.44. Found: C, 60.72; H, 9.01; N, 5.40.



^{1}H NMR of **222** in DMSO-d_6 at 295 °K

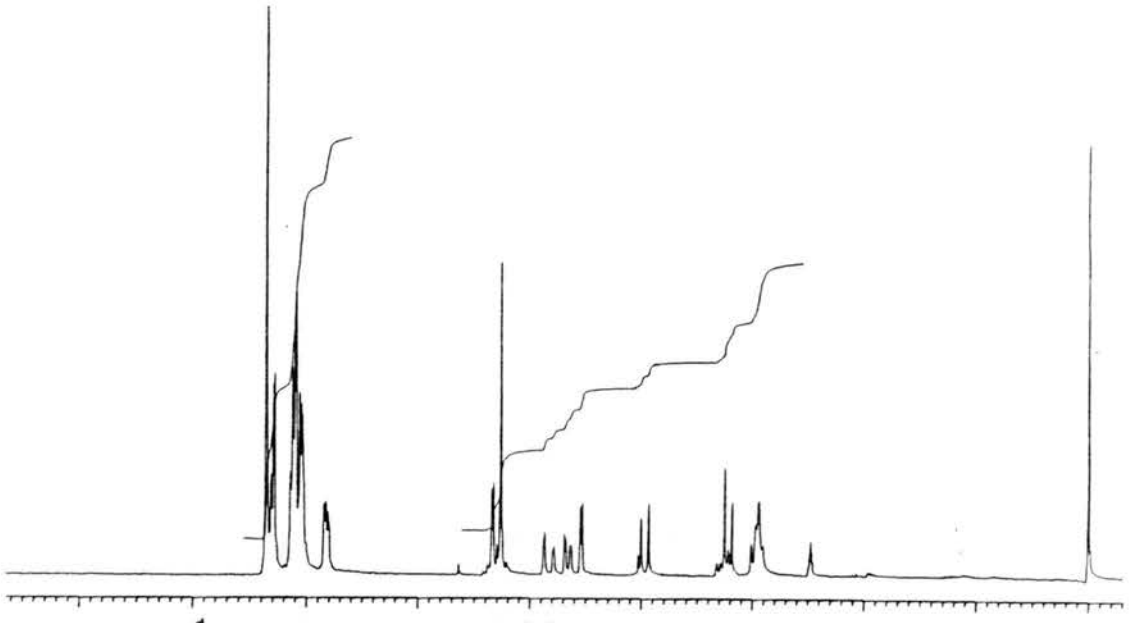


209 223

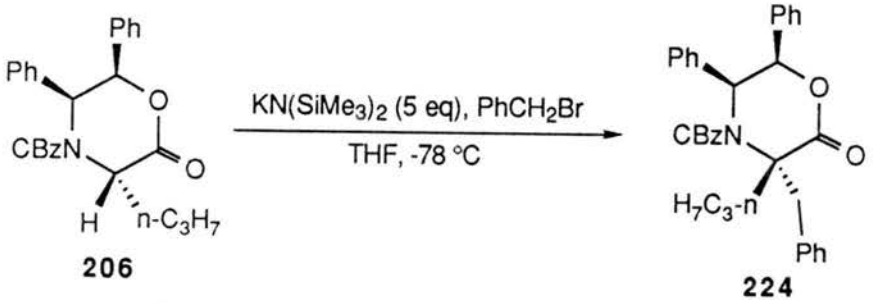
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-benzyl-3-(2'-propenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (223)

To a stirred solution of **209** (50 mg, 0.117 mmol, 1 equiv) and benzyl bromide (70 µl, 0.589 mmol, 5 equiv) in THF (1 ml) was added potassium bis(trimethylsilyl)amide (251 µl, 0.351 mmol, 3 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 51 mg (84%) of **223** as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.90-3.00 (1H, m), 3.19-3.32 (1H, m), 3.23 (1H, 1/2 ABq, J = 13.58 Hz), 3.97 (1H, 1/2 ABq, J = 13.56 Hz), 4.53 (1H, d, J = 3.44 Hz), 4.61-4.86 (2H, m), 5.19-5.41 (1H, m), 5.26 (2H, s), 5.33 (1H, d, J = 3.29 Hz), 6.79-6.83 (2H, m), 7.02-7.12 (10H, m), 7.28-7.36 (8H, m); IR (NaCl, CH_2Cl_2) 1744, 1702 cm^{-1}; $[\alpha]^{25}_D$ +126.9° (c 1.38, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 78.63; H, 5.87; N, 2.67.



^{1}H NMR of **223** in DMSO-d_6 at 393 °K

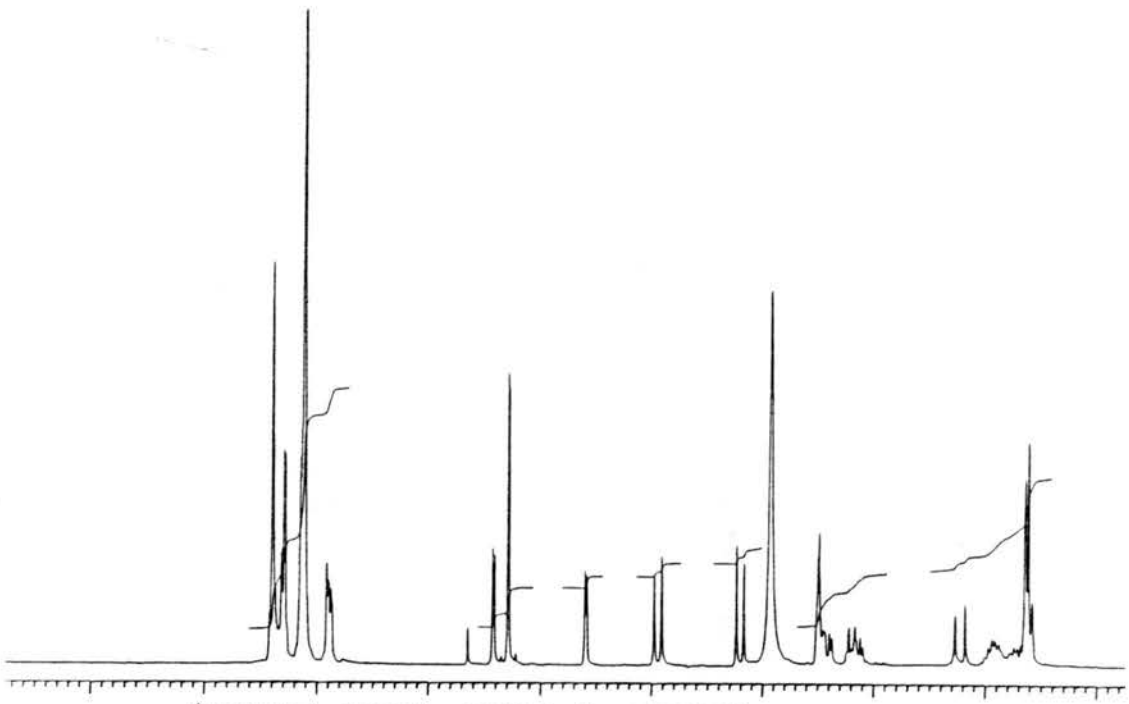


206 **224**

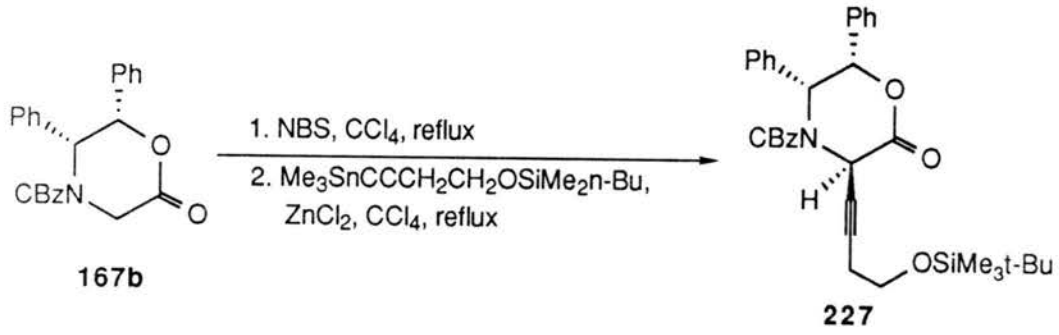
(3S,5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-benzyl-3-propyl -2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (224)

To a stirred solution of **206** (44 mg, 0.102 mmol, 1 equiv) and benzyl bromide (121 µl, 1.02 mmol, 10 equiv) in THF (1 ml) was added potassium bis(trimethylsilyl)amide (366 µl, 0.512 mmol, 5 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 30 min the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated by PTLC on silica gel to afford 45 mg (85%) of **224** as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.61 (3H, t, J = 6.11 Hz), 0.62-0.79 (1H, m), 0.85-1.04 (1H, m), 2.10-2.24 (1H, m), 2.37-2.52 (1H, m), 3.20 (1H, 1/2 ABq, J = 13.51 Hz), 3.94 (1H, 1/2 ABq, J = 13.53 Hz), 4.59 (1H, d, J = 3.33 Hz), 5.25 (1H, 1/2 ABq, J = 12.30 Hz), 5.31 (1H, 1/2 ABq, J = 12.48 Hz), 5.42 (1H, d, J = 3.48 Hz), 6.86-6.92 (2H, m), 7.05-7.42 (18H, m); IR (NaCl, CH_2Cl_2) 1744, 1703 cm^{-1}; $[\alpha]^{25}_D$ +125.4° (c 1.07, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.76; H, 6.33; N, 2.67.



^{1}H NMR of **224** in DMSO-d_6 at 393 °K



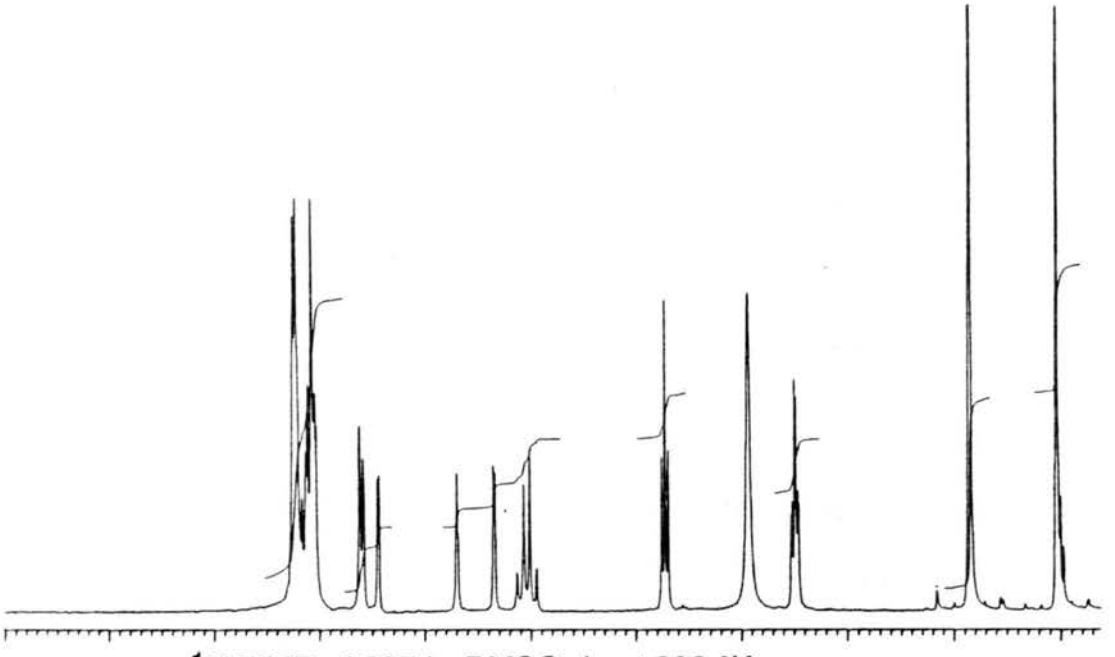
167b **227**

(3R,5R,6S) - 4- (Benzyloxycarbonyl) -5,6- diphenyl -3- (4'- t-butyl-dimethylsiloxy-1'-butynyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (227)

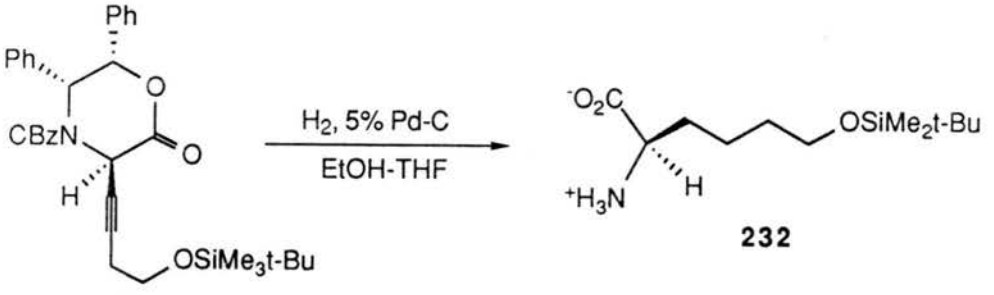
To a refluxing solution of **167b** (2.5 g, 6.46 mmol, 1 equiv) in CCl_4 (700 ml) was added N-bromosuccinimide (1.38 g, 7.75 mmol, 1.2 equiv). After refluxed further 1 hr, the reaction mixture was cooled down to 0 °C and the generated succinimide was filtered. The filtrate was brought to reflux and zinc chloride (9.7 ml, 9.7 mmol, 1.5 equiv, 1 M solution in THF) was added to the solution, followed by addition of 4-t-butyldimethylsiloxy-1-butynyltrimethyl tin (2.7 g, 7.76 mmol, 1.2 equiv). After 5 min the reaction mixture was cooled down and poured into water. The organic layer was separated and the aqueous layer was extracted 3 × with CH_2Cl_2. The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated, separated in column chromatography on silica gel to afford 1.73 g (48%) of **227** as white solid.

^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.03 (6H, s), 0.85 (9H, s), 2.47-2.53 (2H, m), 3.73 (2H, t, J = 6.35 Hz), 4.98 (1H, 1/2 ABq, J = 12.69 Hz), 5.11 (1H, 1/2 ABq, J = 12.90 Hz), 5.35 (1H, d, J = 3.07 Hz), 5.71 (1H, s), 6.46 (1H, d, J = 3.15 Hz), 6.58-6.64 (2H, m), 7.08-7.28 (8H, m); IR (NaCl, CH_2Cl_2) 1765, 1710 cm^{-1}; mp 92-94 °C; $[\alpha]^{25}D$ -2.2° (c 0.54, CH_2Cl_2). Anal.

(recrystallized from Et_2O/hexanes) Calcd for $C_{34}H_{43}NO_5Si$: C, 71.67; H, 6.90; N, 2.46. Found: C, 71.75; H, 6.90; N, 2.44.



^1H NMR of **227** in DMSO-d_6 at 393 °K

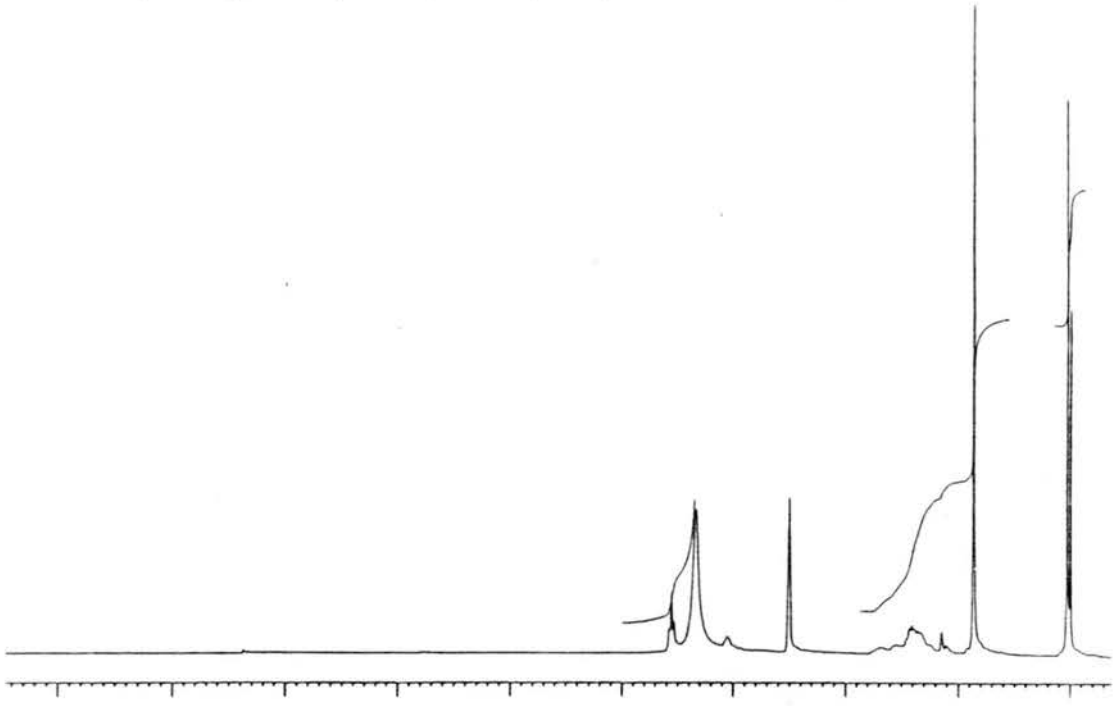


227 **232**

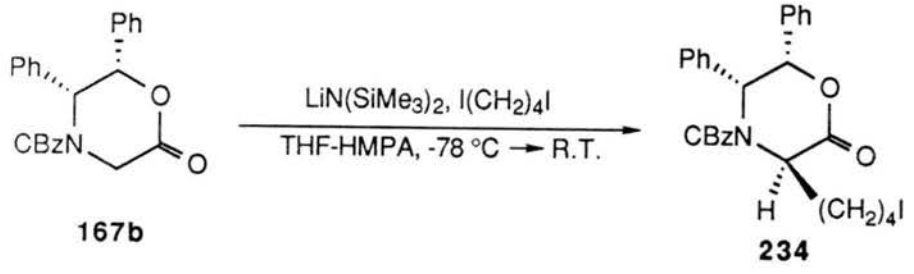
(2R)-2-Amino-6-(t-butyldimethyl)siloxyhexanoic acid (232)

To a solution of **227** (363 mg, 0.637 mmol, 1 equiv) in THF and EtOH (6 ml, 1:1) was added 5 % palladium on activated charcoal (136 mg, 0.064 mmol, 0.1 equiv). The reaction mixture was hydrogenated for 8 hr at atmospheric pressure. The mixture was then filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield 135 mg (81%) of **232** as white solid. This material was converted into **233** without further purification.

^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 0.04 (6H, s), 0.96 (9H, s), 1.29-1.76 (6H, m), 3.06 (1H, m), 3.58 (2H, t).



^{1}H NMR of **232** in DMSO-d_6 at 295 °K



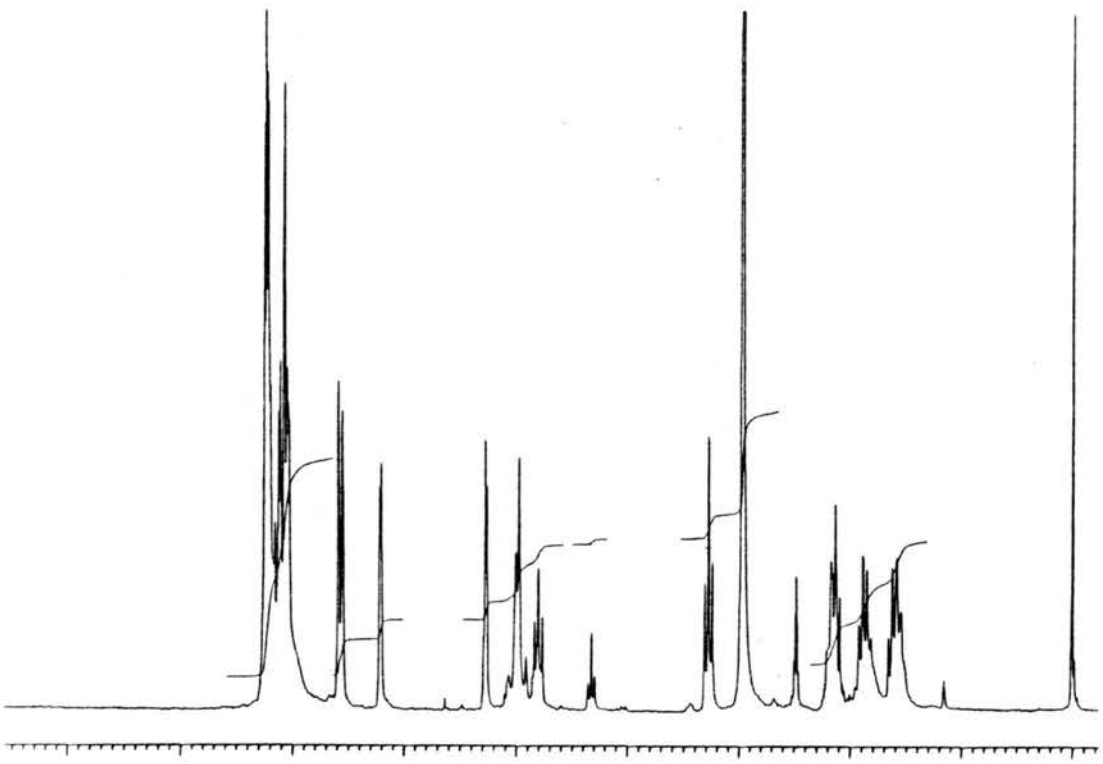
167b **234**

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(4'-iodobutyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (234)

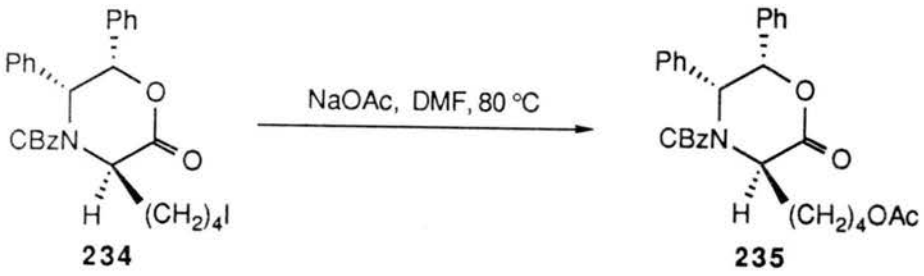
To a stirred solution of **167b** (1.5 g, 3.87 mmol, 1 equiv) and 1,4-diiodobutane (2.55 ml, 19.34 mmol, 5 equiv) in THF (130 ml) and HMPA (13 ml) was added lithium bis(trimethylsilyl)amide (5.8 ml, 5.8 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at -78 °C. After 30 min the dry ice bath was removed. After further 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over

anhydrous magnesium sulfate, filtered, concentrated and crystalized in hexanes to afford 1.73 g (78.6%) of **234** as yellowish solid. The antipode was obtained in 61% yield.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.55-1.66 (2H, m), 1.81-1.93 (2H, m), 2.10-2.22 (2H, m), 3.01 (2H, t, J = 6.83 Hz), 4.82 (1H, t, J = 5.72 Hz), 4.94 (1H, 1/2 ABq, J = 12.50 Hz), 5.05 (1H, 1/2 ABq, J = 12.28 Hz), 5.29 (1H, d, J = 3.01 Hz), 6.01 (1H, d, J = 2.98 Hz), 6.53-6.59 (2H, m), 7.01-7.26 (13H, m); IR (NaCl, CH_2Cl_2) 1756, 1705 cm^{-1}; mp 163-164 °C; $[\alpha]^{25}_D$ +22.9° (c 1.63, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{28}H_{28}INO_4$: C, 59.06; H, 4.96; N, 2.46. Found: C, 59.26; H, 5.16; N, 2.50.



^{1}H NMR of **234** in DMSO-d_6 at 393 °K

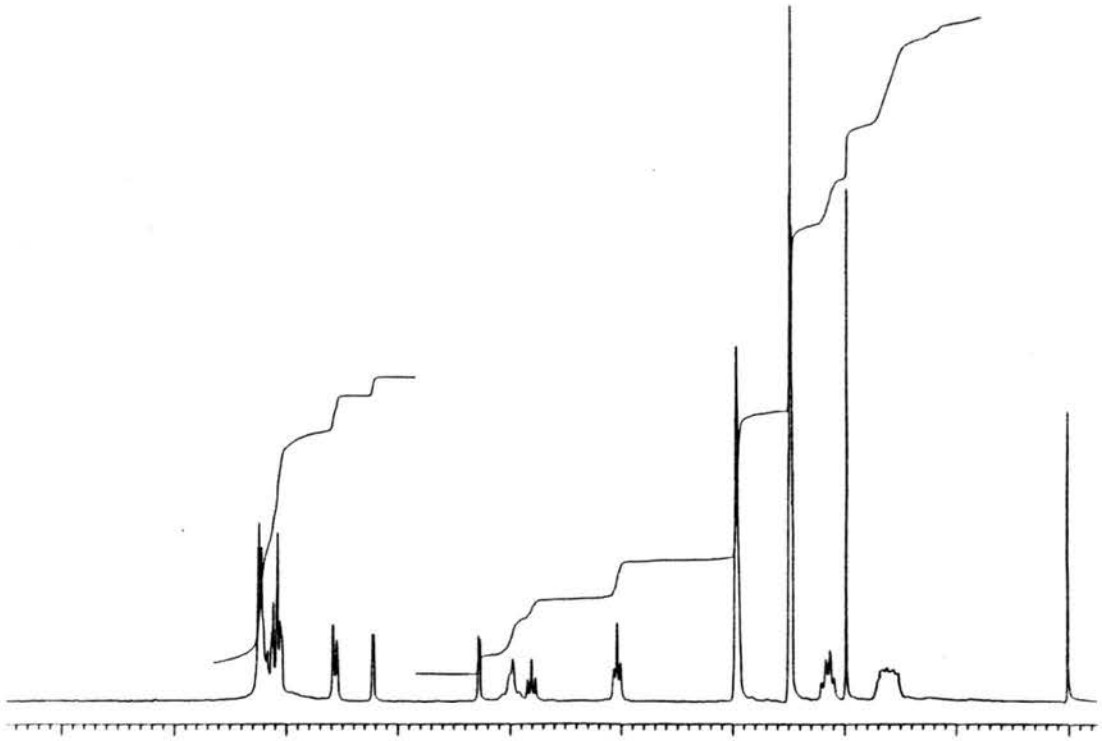


234 235

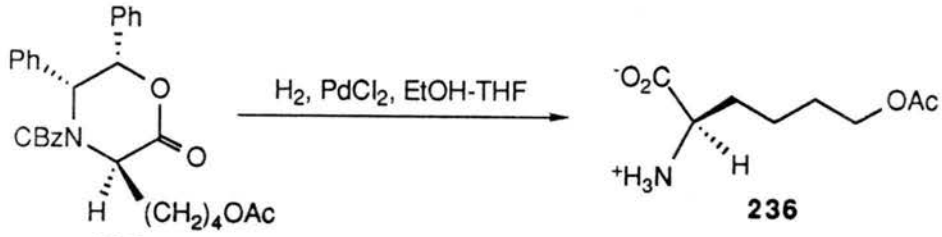
(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(4'-acetyloxy-butyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (235)

To a solution of **234** (1.58 g, 2.77 mmol, 1 equiv) in DMF (100 ml) was added sodium acetate (2.27 g, 27.7 mmol, 10 equiv). The reaction mixture was heated to 80 °C. After 4 hr the reaction mixture was cooled down, poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated in radial chromatography on silica gel to afford 1.12 g (80.6%) of **235** as white solid. The antipode was obtained in 85.8% yield.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.48-1.73 (4H, m), 1.99 (3H, s), 2.15 (2H, q, J = 7.81 Hz), 4.03 (2H, t, J = 6.25 Hz), 4.80 (1H, t, J = 7.36 Hz), 4.90-5.19 (2H, m), 5.27 (1H, d, J = 3.03 Hz), 6.22 (1H, d, J = 3.03 Hz), 6.53-6.59 (2H, m), 7.02-7.27 (13H, m); IR (NaCl, CH_2Cl_2) 1756, 1735, 1704 cm^{-1}; mp 124-125 °C; $[\alpha]^{25}_D$ +35.3° (c 1.41, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.91; H, 6.23; N, 2.79.



^{1}H NMR of **235** in DMSO-d_6 at 393 °K



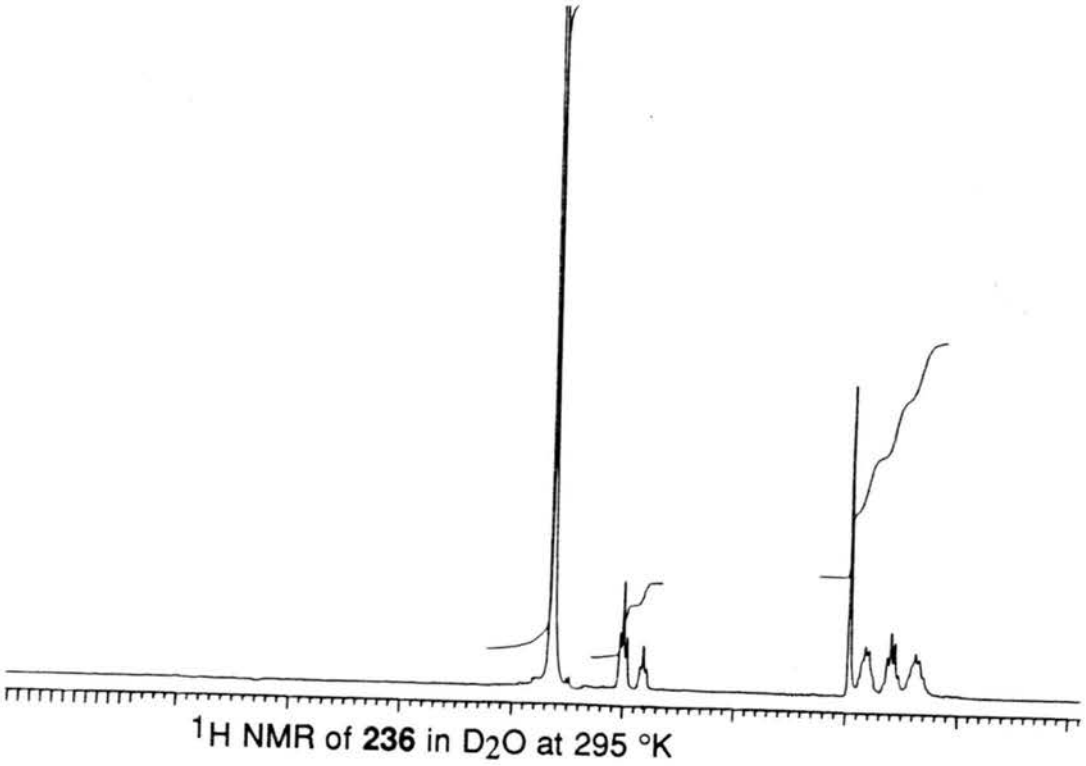
235 **236**

(2R)-2-Amino-6-acetyloxyhexanoic acid (236)

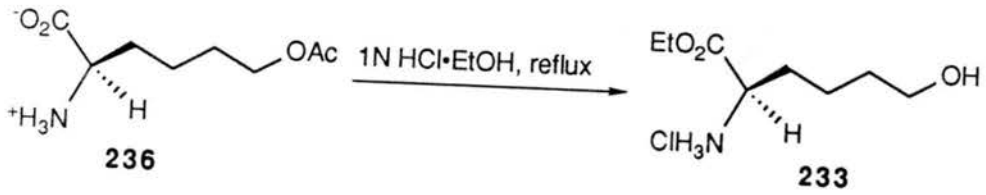
To a solution of **235** (559 mg, 1.11 mmol, 1 equiv) in THF and EtOH (3 ml, 1:2) was added palladium chloride (59.3 mg, 0.33 mmol, 0.3 equiv). The reaction mixture was hydrogenated at 50 psi for 20 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated and triturated with Et_2O to yield **236** as white solid: 97 % ee. The antipode: 100 % ee.

^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.25-1.38 (2H, m), 1.48-1.60 (2H, m), 1.70-1.84 (2H, m), 1.92 (3H, s), 3.77 (1H, t, J = 6.12 Hz), 3.96 (2H, t, J =

6.48 Hz); IR (ZnS, MeOH) 3030, 1732, 1697(shoulder) cm^{-1}; mp 190-192 °C (decom.); $[\alpha]^{25}_D$ -12.8° (c 0.5, 1N HCl).



^1H NMR of **236** in D_2O at 295 °K

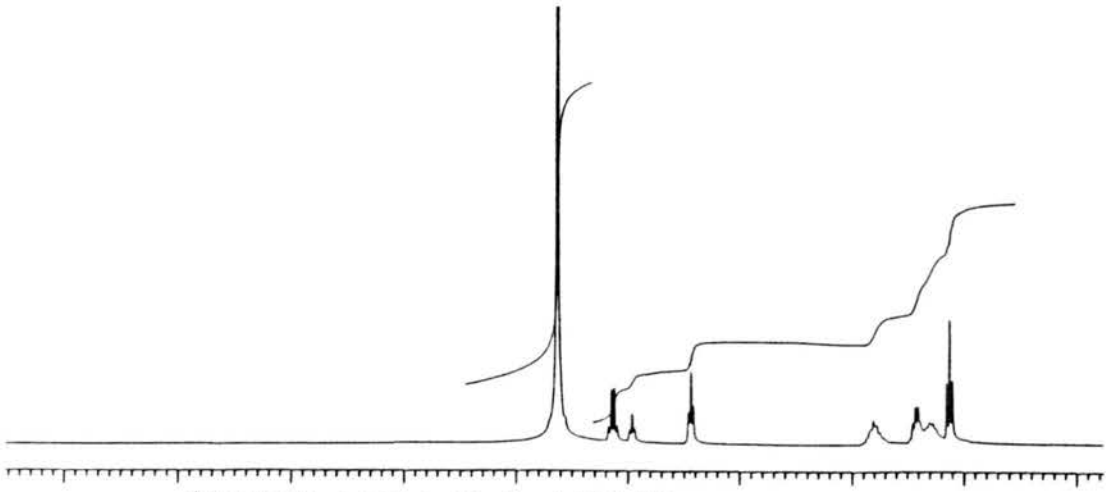


236 **233**

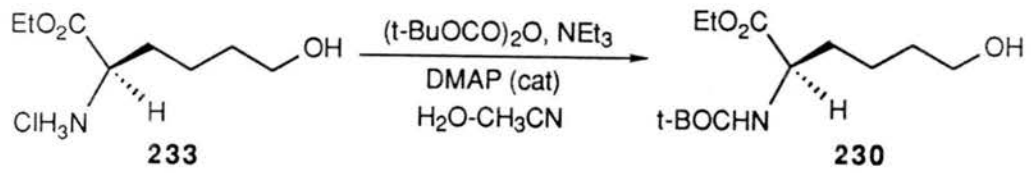
(2R)-Ethyl (2-amino-6-hydroxy)heptanoate Hydrochloride (233)

The obtained amino acid **232** or **236** was refluxed in 1N HCl•EtOH. After 2 hr the ethanol was evaporated and the residue was dried completely in vacuo line to afford 232 mg (98.3%, 2 steps) of **233** as colorless oil. The antipode was obtained in 97.7% yield.

^1H NMR (270 MHz, D_2O, vs HOD) δ 1.13 (3H, t, J = 7.11 Hz), 1.21-1.48 (4H, m), 1.72-1.89 (2H, m), 3.44 (2H, t, J = 6.16 Hz), 3.96 (1H, t, J = 6.31 Hz), 4.13 (2H, q, J = 7.15 Hz); IR (ZnS, EtOH) 3346, 1744 cm^{-1}; $[\alpha]^{25}_D$ -8.2° (c 1.32, H_2O).



^{1}H NMR of **233** in D_2O at 295 °K



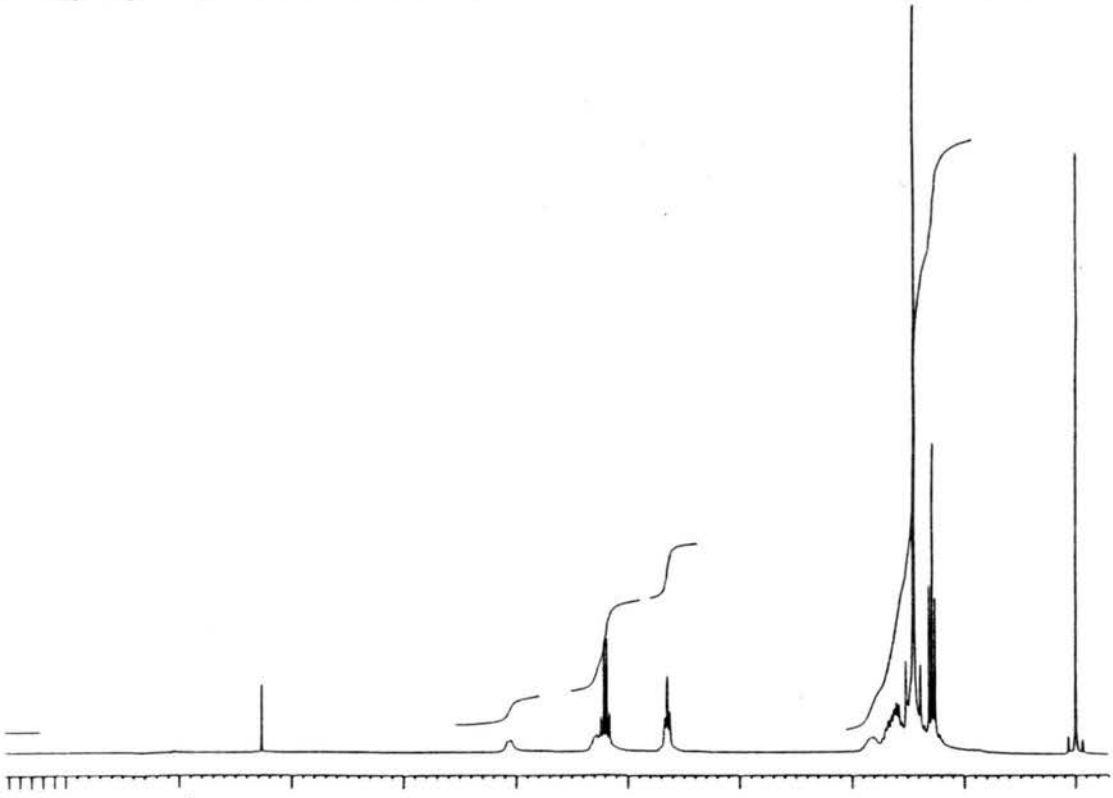
233 **230**

(2R)-Ethyl 2-(t-butyloxycarbonyl)amino-6-hydroxyheptanoate(230)

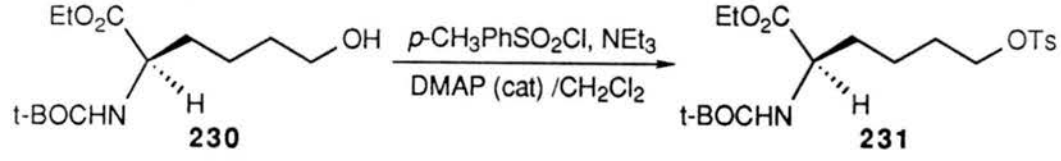
To a stirred solution of **233** (382 mg, 1.81 mmol, 1 equiv) in H_2O (4.5 ml) was added a solution of di-t-butyl dicarbonate (591 mg, 2.71 mmol, 1.5 equiv) in CH_3CN (4.5 ml) followed by addition of triethylamine (755 ml, 5.42 mmol, 3 equiv) and DMAP (44 mg, 0.36 mmol, 0.2 equiv). After 24 hr the reaction mixture was poured into ethyl acetate and water was separated. The organic layer was washed with 0.5 M citric acid, H_2O and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 392 mg (83.5%) of **230** as light amber oil. The antipode was obtained in 80.5% yield.

^{1}H NMR (270 MHz, $CDCl_3$, vs TMS) δ 1.28 (3H, t, J = 7.13 Hz), 1.45 (9H, s), 1.53-1.91 (6H, m), 3.65 (2H, t, J = 6.26 Hz), 4.19 (2H, q, J = 7.14 Hz), 4.22-4.35 (1H, m), 5.06 (1H, d, D_2O exch., J = 7.84 Hz); IR (NaCl, $CDCl_3$) 3436

(shoulder), 3360, 1732, 1710 cm^{-1} ; $[\alpha]^{25}_D$ -3.9° (c 4.5, CH_2Cl_2). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.64; H, 8.97; N, 5.13.



^1H NMR of **230** in $CDCl_3$ at 295 °K



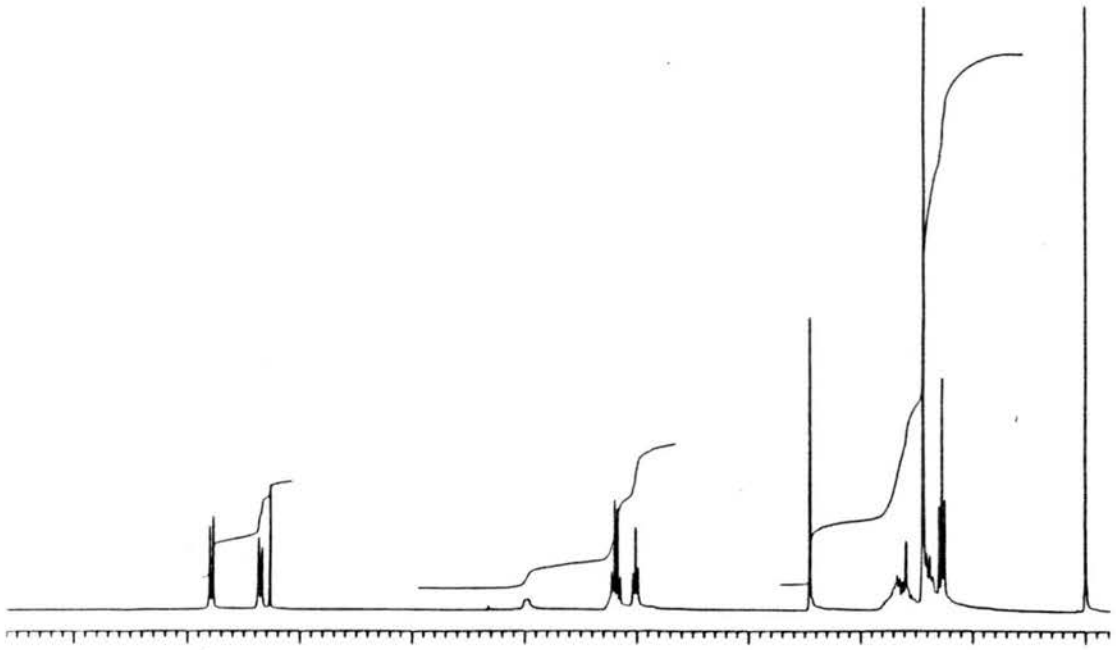
230 **231**

(2R)-Ethyl 2-(t-butyloxycarbonyl)amino-6-(*p*-toluenesulfonyloxy) heptanoate (231)

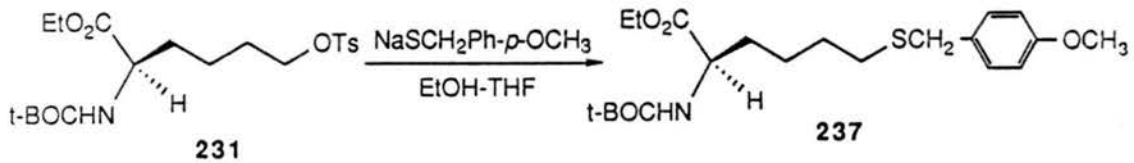
To a stirred solution of **230** (1.1 g, 3.99 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was added *p*-toluenesulfonyl chloride (1.5 g, 7.87 mmol, 2 equiv) followed by addition of triethylamine (1.1 ml, 7.89 mmol, 2 equiv) and DMAP (98 mg, 0.80 mmol, 0.2 equiv). After 2 hr the reaction mixture was poured into CH_2Cl_2. The methylene chloride solution was washed 3 × with 0.5 M citric acid, H_2O and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and

separated in radial chromatography on silica gel to afford 1.61 g (93.8%) of **231** as light amber oil. The antipode was obtained in 94.4% yield.

^{1}H NMR (270 MHz, $CDCl_3$, vs TMS) δ 1.27 (3H, t, J = 7.17 Hz), 1.34-1.42 (2H, m), 1.45 (9H, s), 1.51-1.79 (4H, m), 2.45 (3H, s), 4.01 (2H, t, J = 6.39 Hz), 4.18 (2H, q, J = 7.14 Hz), 4.21-4.25 (1H, m), 4.98 (1H, d, D_2O exch., J = 7.76 Hz), 7.34 (2H, d, J = 8.31 Hz), 7.79 (2H, d, J = 8.29 Hz); IR (NaCl, $CDCl_3$) 3381, 1738, 1710, 1362, 1177 cm^{-1} ; $[\alpha]^{25}_D$ -6.1° (c 1.29, CH_2Cl_2). Anal. Calcd for $C_{20}H_{31}NO_7S$: C, 55.92; H, 7.28; N, 3.26. Found: C, 55.77; H, 7.20; N, 3.29.



^{1}H NMR of **231** in $CDCl_3$ at 295 °K



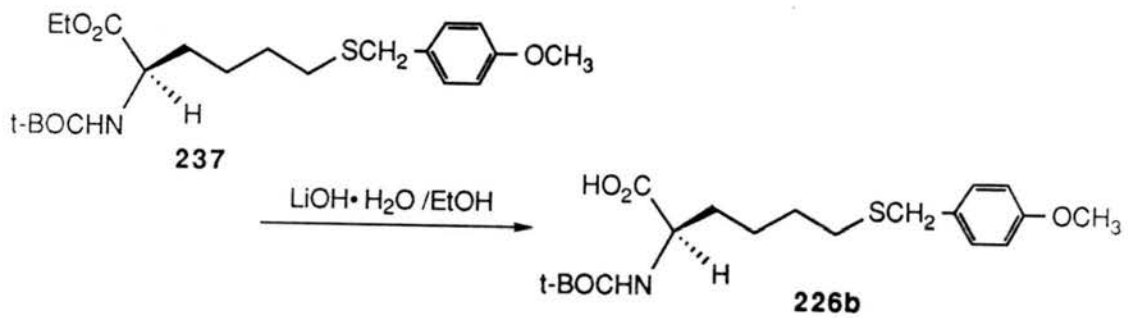
231 **237**

(2R)-Ethyl 2-(t-butyloxycarbonyl)amino-6-(*p*-methoxybenzyl)thiono heptanoate (237)

To a vigorously stirred suspension of sodium ethoxide (69.4 mg, 1.02 mmol, 3 equiv) in EtOH (5 ml) was added (*p*-methoxy)-α-toluene thiol (142 ml,

1.02 mmol, 3 equiv). After 20 min a solution of **231** (146 mg, 0.34 mmol, 1 equiv) in THF (5ml) was added to the reaction mixture. After 45 min solvent was evaporated off and the residue was diluted with THF. The white precipitate was filtered. The filtrate was concentrated and separated in radial chromatography to afford 126.5 mg (90.4%) of **237** as colorless oil.

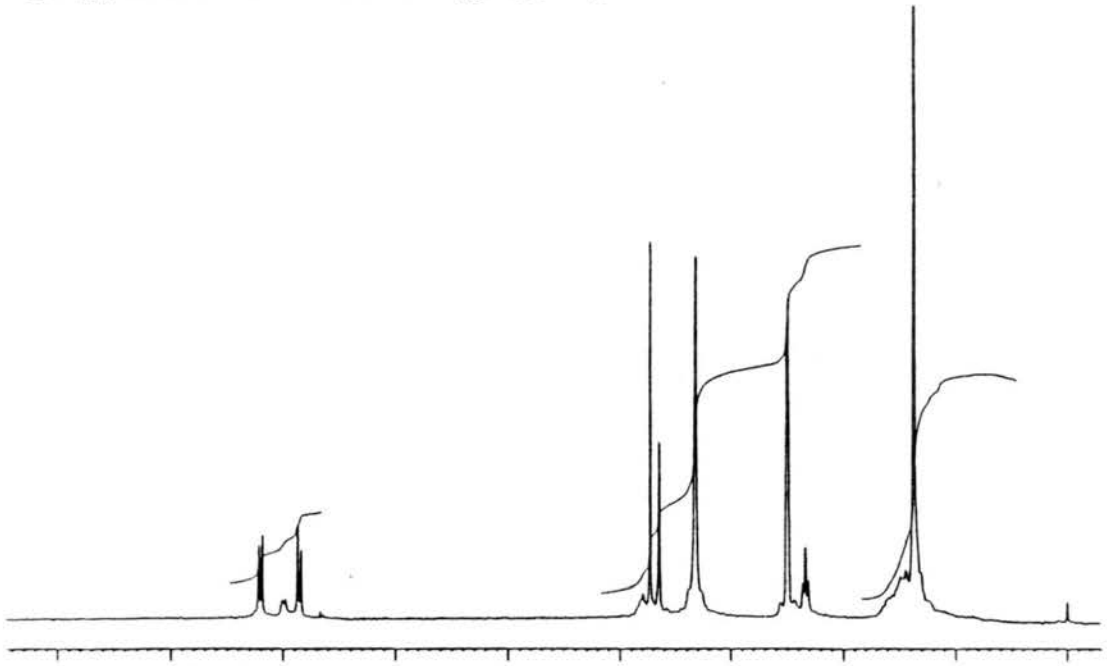
^{1}H NMR (270 MHz, $CDCl_3$, vs TMS) δ 0.82-0.91 (2H, m), 1.27 (3H, t), 1.45 (9H, s), 1.24-1.60 (4H, m), 2.40 (2H, t), 3.74 (2H, s), 3.81 (3H, s), 4.20 (2H, q), 4.22-4.32 (1H, m), 4.99 (1H, d, D_2O exch.), 6.85 (2H, d), 7.22 (2H, d); IR (NaCl, $CDCl_3$) 3370, 1738, 1710 cm^{-1}; mass spectrum (NH_3, CI) *m/e* 412 (M^++1, 3.4)



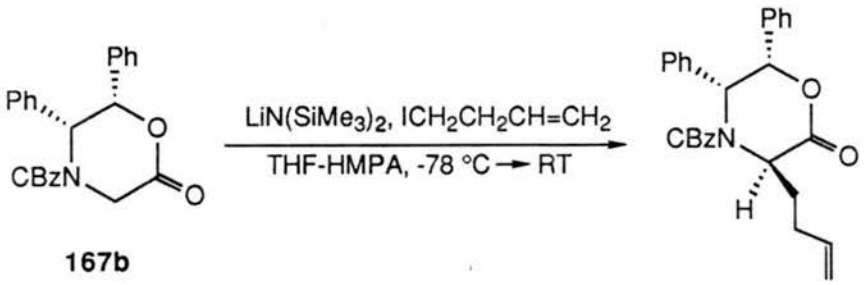
(2R)-2-(t-Butyloxycarbonyl)amino-6-(*p*-methoxybenzyl)thiono-hexanoic acid (226b)

To a stirred solution of **237** (1.54 g, 3.74 mmol, 1 equiv) in EtOH (120 ml) was added lithium hydroxide monohydrate (785 mg, 18.71 mmol, 5 equiv). After 15 hr ethanol was evaporated off and the residue was diluted with water. The aqueous solution was acidified to pH 2 with 1N HCl, extracted 3 × with EtOAc. The combined organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated and separated in radial chromatography on silica gel to afford 1.31 g (91.3%) of **226b** as light amber oil.

^{1}H NMR (270 MHz, DMSO-d_6, vs TMS) δ 1.37 (9H, s), 1.20-1.69 (6H, m), 2.34 (2H, t, J = 7.03 Hz), 3.65 (2H, s), 3.73 (3H, s), 3.74-3.85 (1H, m), 6.86 (2H, d, J = 8.47 Hz), 6.99 (1H, d, D_2O exch., J = 8.72 Hz), 7.21 (2H, d, J = 8.50 Hz); IR (NaCl, $CDCl_3$) 3335, 1709, 1654 (shoulder) cm^{-1}; $[\alpha]^{25}_D$ -0.7° (c 1.2, CH_2Cl_2); Exact mass calcd for $C_{19}H_{30}NO_5S$ 384.1845, found 384.1841.



^{1}H NMR of **226b** in DMSO-d_6 at 295 °K



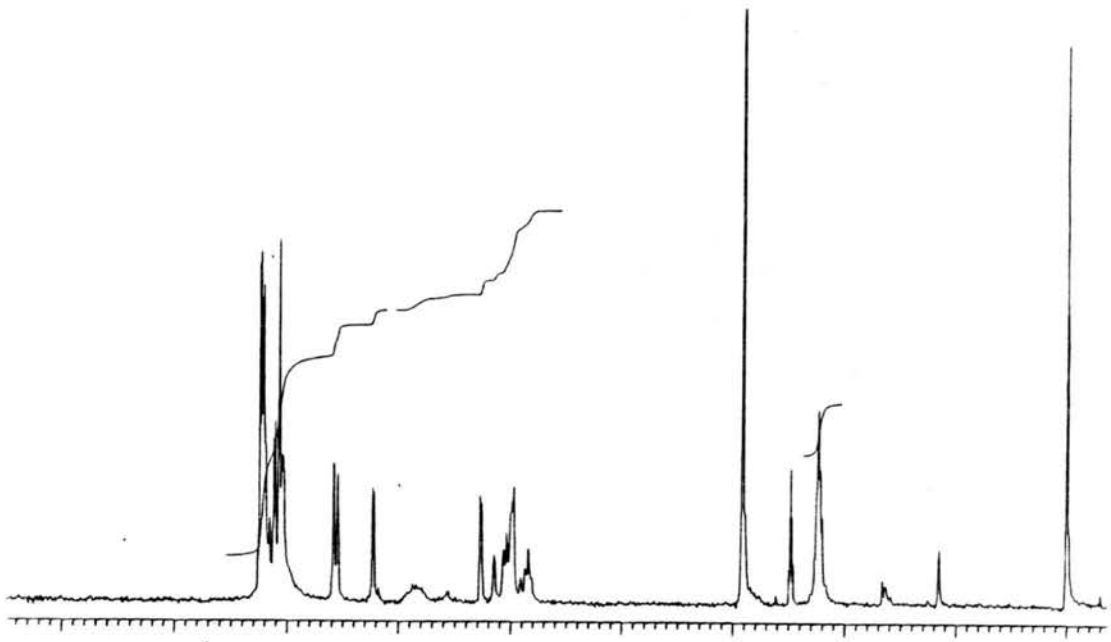
167b **246**

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3'-butenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (246)

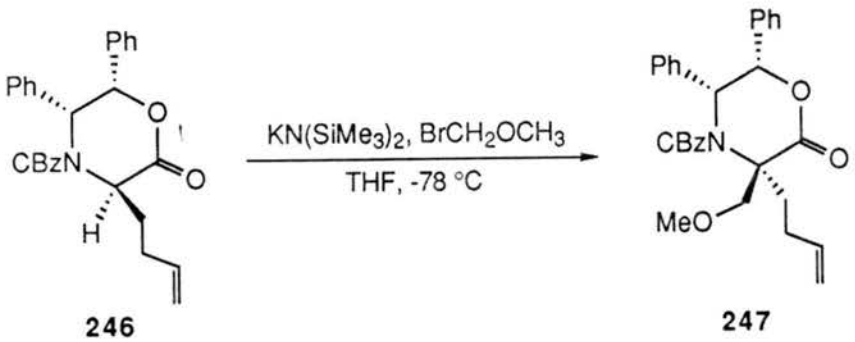
To a stirred solution of **167b** (3 g, 7.7 mmol, 1 equiv) and 4-iodobutene (4.2 ml, 39.35 mmol, 5.1 equiv) in warm THF (90 ml) and HMPA (9 ml) was added lithium bis(trimethylsilyl)amide (13.9 ml, 13.9 mmol, 1.8 equiv, 1 M

solution in THF) dropwise via syringe at -78 °C. After 10 min the dry ice bath was removed. After further 1 hr, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 1.59 g (46.5%) of **246** as white solid. The antipode was obtained in 48.5% yield.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.18-2.31 (4H, m), 4.81-5.16 (5H, m), 5.27 (1H, d, J = 2.93 Hz), 5.77-5.95 (1H, m), 6.22 (1H, d, J = 3.02 Hz), 6.54-6.59 (2H, m), 7.02-7.24 (13H, m); IR (NaCl, CH_2Cl_2) 1747, 1704 cm^{-1}; mp 146-147 °C; $[\alpha]^{25}_D$ +44.1° (c 0.49, CH_2Cl_2), Antipode -45.2° (c 0.42, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd. for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.17; N, 3.17. Found: C, 76.07; H, 6.36; N, 3.20.



^{1}H NMR of **246** in DMSO-d_6 at 393 °K

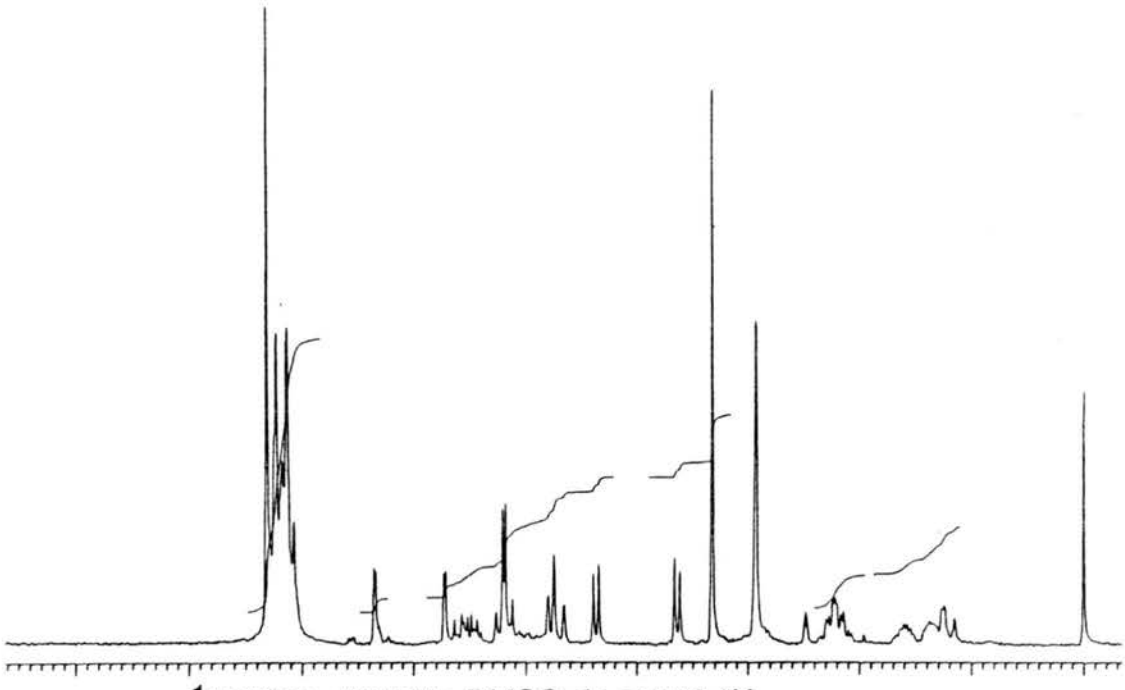


246 247

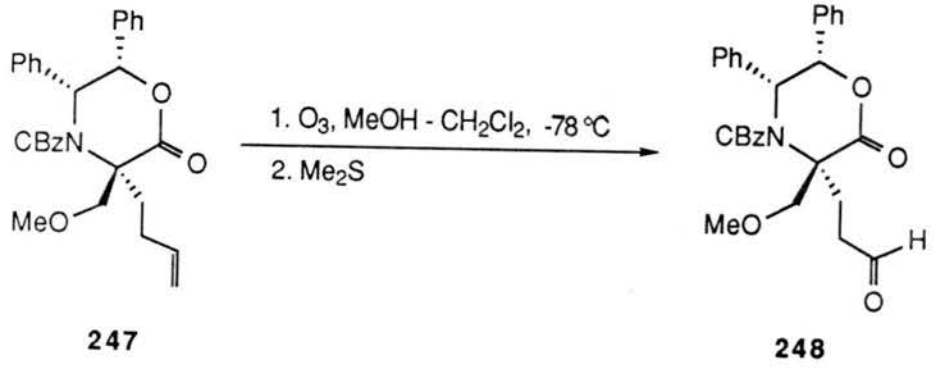
(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3'-butenyl)-3-methoxymethyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (247)

To a stirred solution of **246** (1.1 g, 2.49 mmol, 1 equiv) in THF (15 ml) was added potassium bis(trimethylsilyl)amide (8.9 ml, 12.46 mmol, 5 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 5 min bromomethyl methyl ether (2 ml, 24.9 mmol, 10 equiv) was added to the reaction mixture at -78 °C. After further 50 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 1.17 g (96.7%) of **247** as colorless oil. The antipode was obtained in 88.5 % yield.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.29-1.43 (1H, m), 1.51-1.70 (1H, m), 2.09-2.38 (2H, m), 3.32 (3H, s), 3.64 (1H, 1/2 ABq, J = 9.76 Hz), 4.37 (1H, 1/2 ABq, J = 9.79 Hz), 4.65-4.79 (2H, m), 5.15 (1H, 1/2 ABq, J = 12.31 Hz), 5.24 (1H, 1/2 ABq, J = 12.07 Hz), 5.41-5.64 (1H, m), 5.72 (1H, d, J = 3.32 Hz), 6.35 (1H, d, J = 3.28 Hz), 7.07-7.31 (15H, m); IR (NaCl, CH_2Cl_2) 1746, 1702 cm^{-1}; $[\alpha]^{25}_D$ -49.4° (c 0.35, CH_2Cl_2), Antipode +48.7° (c 0.39, CH_2Cl_2). Exact mass (FAB) calcd. for $C_{30}H_{31}NO_5Li$: 492.236228; found 492.2381.



^{1}H NMR of **247** in DMSO-d_6 at 393 °K



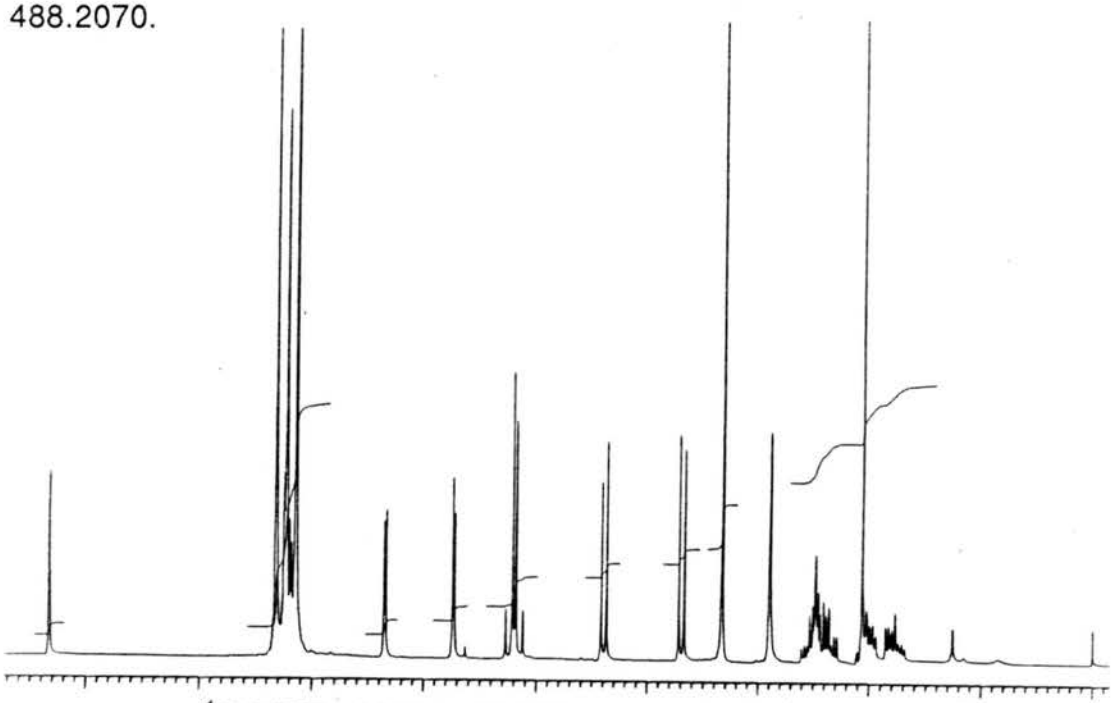
247 **248**

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3'-carbonyl-ethyl)-3-methoxymethyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (248)

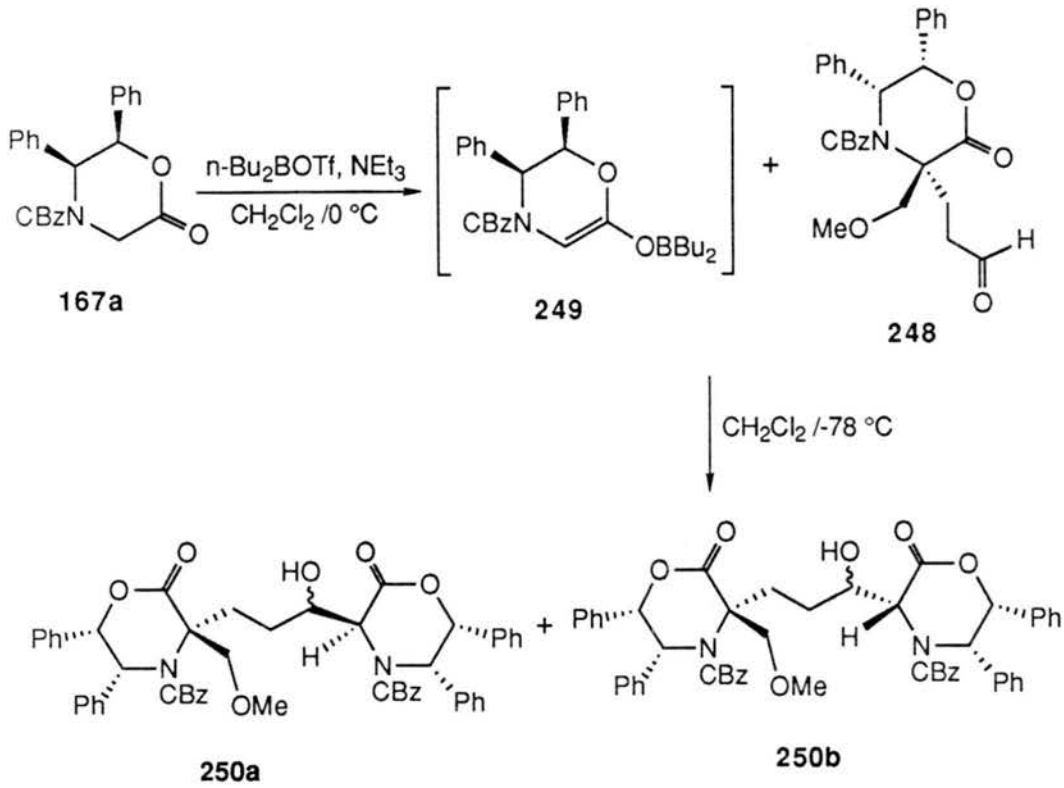
Ozone was bubbled through a solution of **247** (316 mg, 0.651 mmol, 1 equiv) in MeOH-CH_2Cl_2 (10 ml, 1 : 1) until the solution turned to blue (ca. 5 min). Nitrogen gas then was passed through the reaction mixture to remove excess ozone until the solution became colorless. The resulting solution was quenched with excess dimethyl sulfide. After 15 hr the reaction mixture was

concentrated and separated in radial chromatography on silica gel to afford 319 mg (96%) of **248** as colorless oil. The antipode was obtained in 94 % yield.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.69-1.84 (1H, m), 1.95-2.10 (1H, m), 2.28-2.60 (2H, m), 3.32 (3H, s), 3.68 (1H, 1/2 ABq, J = 9.79 Hz), 4.38 (1H, 1/2 ABq, J = 9.81 Hz), 5.14 (1H, 1/2 ABq, J = 12.35 Hz), 5.24 (1H, 1/2 ABq, J = 12.35 Hz), 5.72 (1H, d, J = 3.40 Hz), 6.35 (1H, d, J = 3.44 Hz), 7.14-7.32 (15H, m), 9.32 (1H, s); IR (NaCl, CH_2Cl_2) 1745, 1722 (shoulder), 1701 cm^{-1}; $[\alpha]^{25}_D$ -79.9° (c 1.2, CH_2Cl_2), Antipode +80.4° (c 0.7, CH_2Cl_2). Exact mass (FAB) calcd. for $C_{29}H_{30}NO_6$: 488.207314; (M^++H); found: 488.2070.



^{1}H NMR of **248** in DMSO-d_6 at 393 °K



167a 249 248

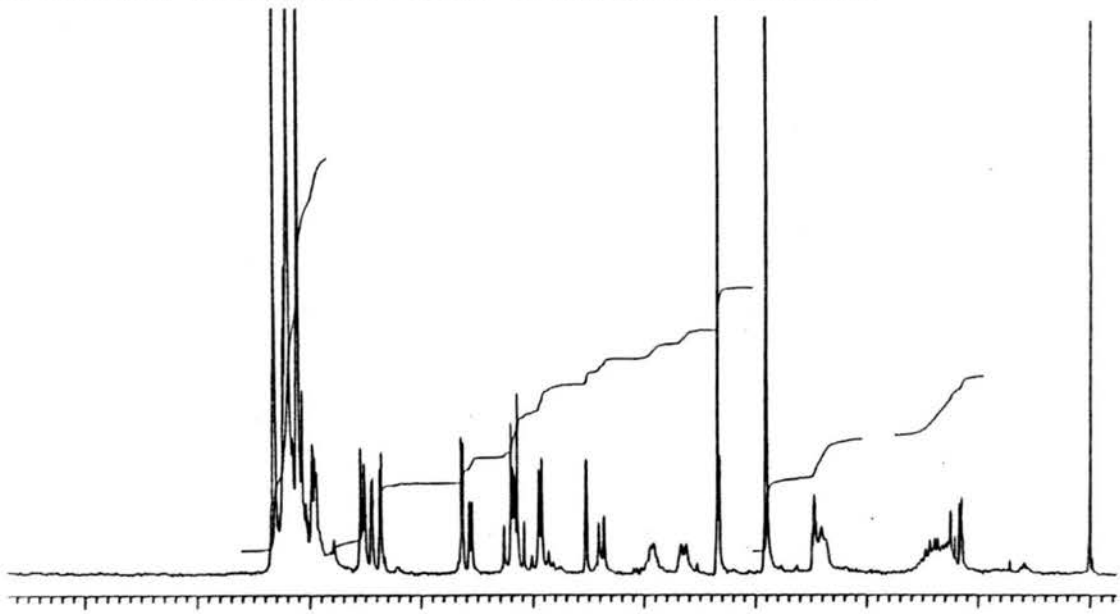
250a 250b

250a and 250b

To a stirred solution of **167a** (445 mg, 1.15 mmol, 1 equiv) in CH_2Cl_2 (8 ml) was added dibutylboron triflate (2.3 ml, 2.30 mmol, 2 equiv, 1 M solution in CH_2Cl_2) followed by addition of triethylamine (320 µl, 2.30 mmol, 2 equiv) at 0 °C. After 20 min the reaction mixture was cooled down to -78 °C and a CH_2Cl_2 (11 ml) solution of **248** (1.12 g, 2.297 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with phosphate buffer solution (pH = 6.9), poured into water. The aqueous layer was extracted 3× with CH_2Cl_2. The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 613 mg (61%) of **250a** as white solid and 41 mg (4.1%) of **250b** as white solid.

250a:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.32-1.55 (2H, m), 2.36-2.47 (2H, m), 3.34 (3H, s), 3.65 (1H, 1/2 ABq, J = 9.86 Hz), 3.89-3.99 (1H, m), 4.38 (1H, 1/2 ABq, J = 9.74 Hz), 4.52 (1H, d, J = 1.89 Hz), 4.89 (1H, 1/2 ABq, J = 12.66 Hz), 4.98 (1H, 1/2 ABq, J = 12.52 Hz), 5.11 (1H, 1/2 ABq, J = 12.47 Hz), 5.18 (1H, d, J = 3.21 Hz), 5.23 (1H, 1/2 ABq, J = 12.39 Hz), 5.56 (1H, d, D_2O exch., J = 5.23 Hz), 5.63 (1H, d, J = 3.59 Hz), 6.36 (1H, d, J = 3.50 Hz), 6.44 (1H, d, J = 3.14 Hz), 6.52 (2H, d, J = 6.76 Hz), 6.93-7.34 (28H, m); IR (NaCl, CH_2Cl_2) 3474, 1749, 1704 cm^{-1}; mp 123-125 °C; $[\alpha]^{25}_D$ -7.9° (c 0.92, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{53}H_{50}N_2O_{10}$: C, 72.76; H, 5.76; N, 3.20. Found: C, 72.94; H, 6.02; N, 3.02.

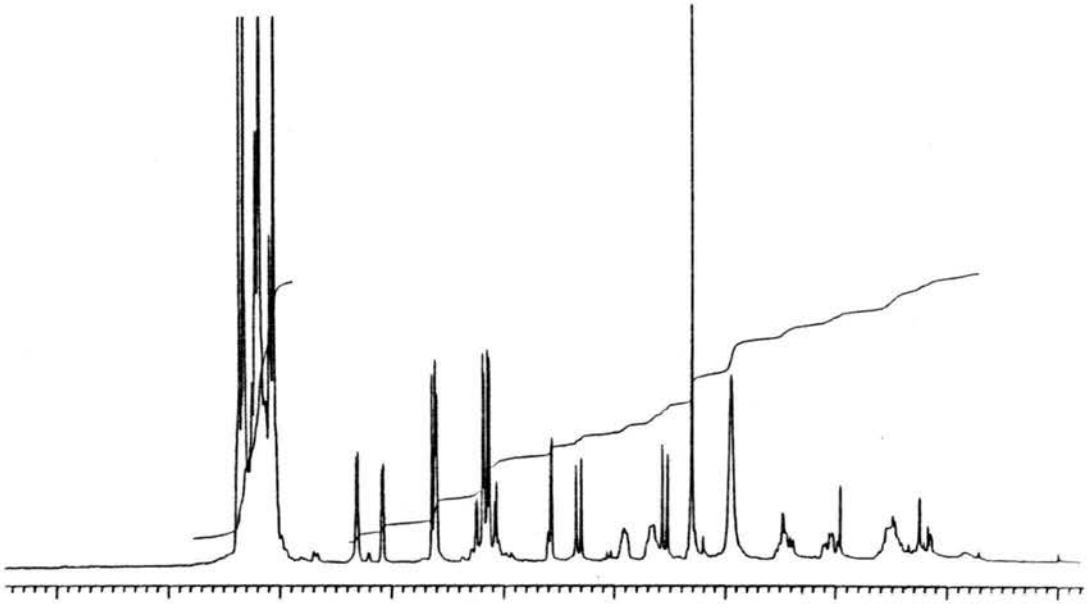


^{1}H NMR of **250a** in DMSO-d_6 at 393 °K

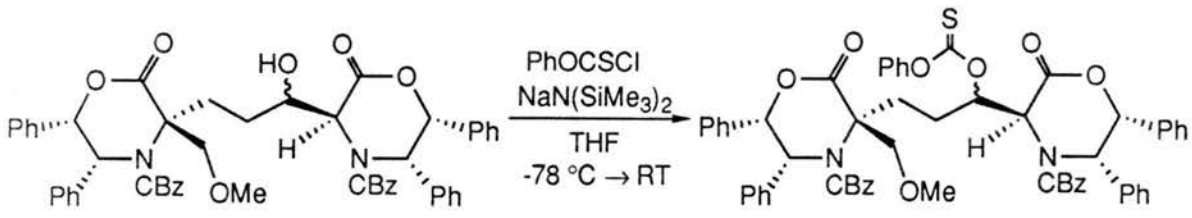
250b:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.41-1.59 (2H, m), 1.96-2.11 (1H, m), 2.39-2.55 (1H, m), 3.35 (3H, s), 3.54 (1H, 1/2 ABq, J = 9.78 Hz), 3.63-3.71 (1H, m), 3.91 (1H, d, D_2O exch., J = 4.79 Hz), 4.33 (1H, 1/2 ABq, J = 9.82 Hz), 4.58 (1H, d, J = 1.96 Hz), 5.11 (1H, 1/2 ABq, J = 12.31 Hz), 5.13 (1H, 1/2 ABq, J = 12.43 Hz), 5.20 (1H, 1/2 ABq, J = 12.39 Hz), 5.22 (1H, 1/2

ABq, J = 12.33 Hz), 5.61 (2H, d, J = 3.23 Hz), 6.08 (1H, d, J = 3.29 Hz), 6.31 (1H, d, J = 3.31 Hz), 7.07-7.39 (30H, m); IR (NaCl, CH_2Cl_2) 3483, 1746, 1702 cm^{-1}; mp 101-103 °C; $[\alpha]^{25}D$ +11.1° (c 0.56, CH_2Cl_2). Exact mass calcd. for $C_{53}H_{51}N_2O_{10}$ (M^++H): 875.35453; found 875.3521.



^1H NMR of **250b** in DMSO-d_6 at 393 °K



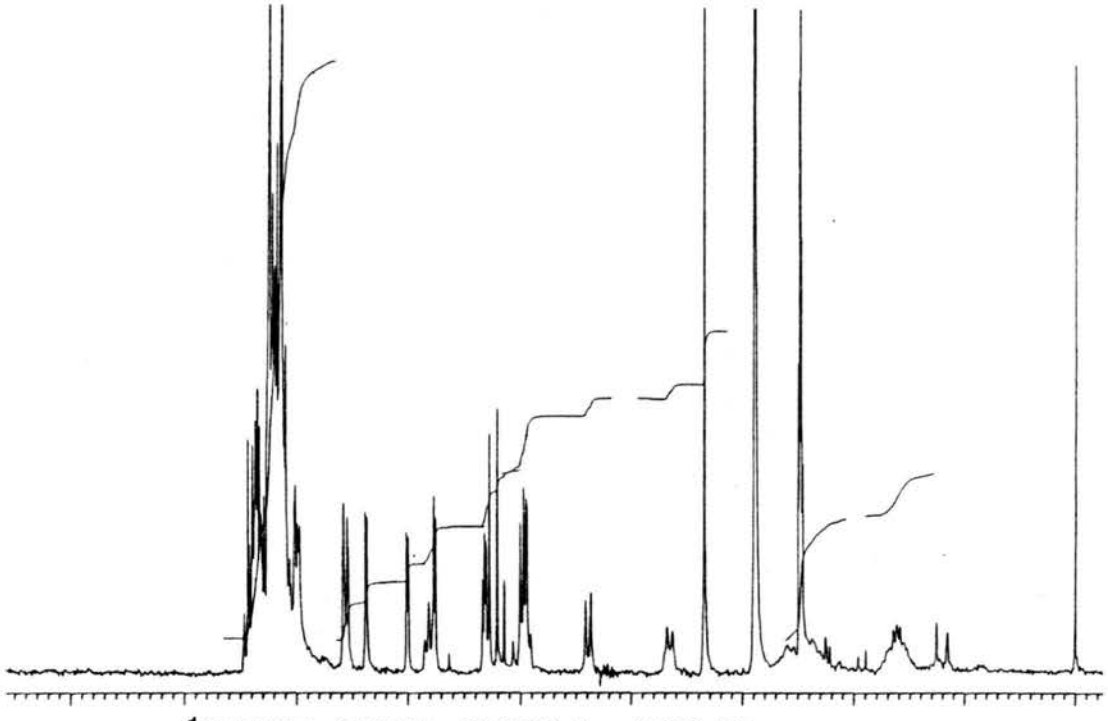
250a **258**

258

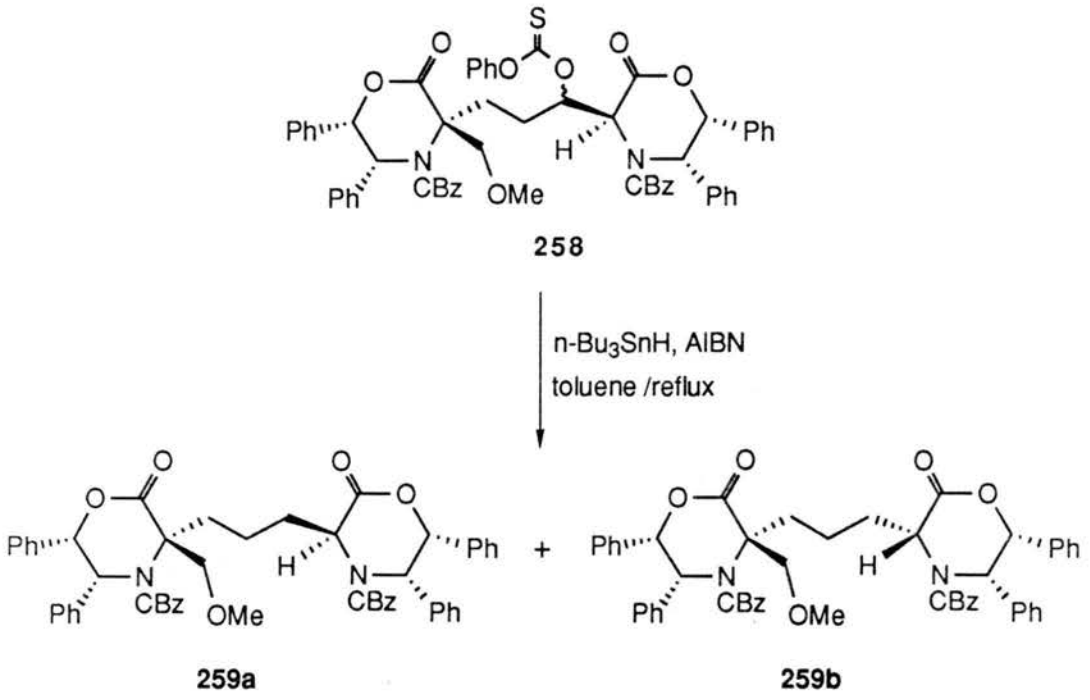
To a solution of **250a** (237 mg, 0.271 mmol, 1 equiv) in THF (4 ml) was added phenyl chlorothionoformate (187 µl, 1.352 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (298 µl, 0.298 mmol, 1.1 equiv, 1 M solution in THF) at -78 °C. After 10 min dry ice bath was removed. After further reaction for 3 hr, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over

anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 170 mg (62%) of **258** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.50-1.76 (2H, m), 2.22-2.65 (2H, m), 3.35 (3H, s), 3.66 (1H, 1/2 ABq, J = 9.56 Hz), 4.38 (1H, 1/2 ABq, J = 9.83 Hz), 4.94 (1H, d, J = 1.66 Hz), 4.94 (1H, 1/2 ABq, J = 12.46 Hz), 5.03 (1H, 1/2 ABq, J = 12.79 Hz), 5.17 (1H, 1/2 ABq, J = 12.31 Hz), 5.30 (1H, 1/2 ABq, J = 12.27 Hz), 5.31 (1H, d, J = 3.15 Hz), 5.75 (1H, d, J = 3.32 Hz), 5.77-5.85 (1H, m), 6.00 (1H, d, J = 3.21 Hz), 6.37 (1H, d, J = 3.34 Hz), 6.56 (2H, d, J = 6.84 Hz), 6.97-7.46 (33H, m); IR (NaCl, CH_2Cl_2) 1754, 1704 cm^{-1};



^{1}H NMR of **258** in DMSO-d_6 at 393 °K



258

259a **259b**

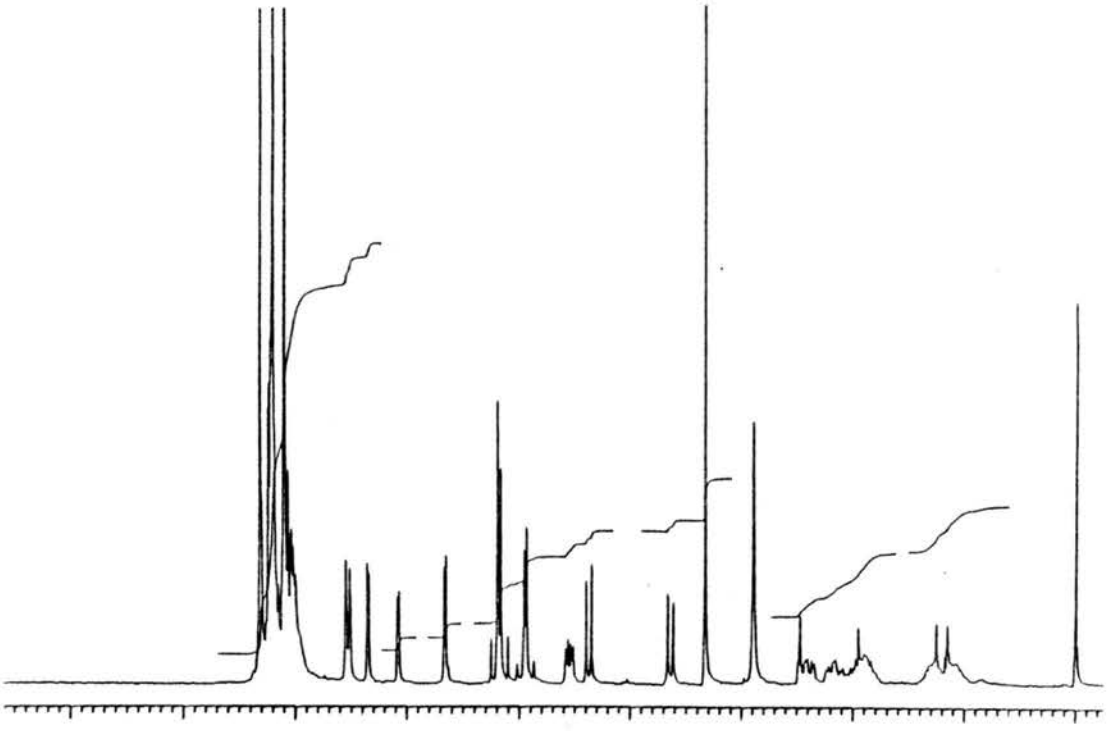
259a and 259b

To a solution of **258** (170 mg, 0.168 mmol, 1 equiv) in toluene was added AIBN (5.5 mg, 0.033 mmol, 0.2 equiv) followed by addition of tributyltin hydride (90 µl, 0.335 mmol, 2 equiv). The resulting solution was brought to reflux. After 3 hr touene was evaporated off and the residue was separated in column chromatography on silica gel to afford 71 mg (49%) of **259a** as white solid and 16 mg (11%) of **259b** as white solid.

259a:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.01-1.18 (1H, m), 1.22-1.38 (1H, m), 1.79-2.03 (2H, m), 2.11-2.25 (1H, m), 2.35-2.48 (1H, m), 3.33 (3H, s), 3.64 (1H, 1/2 ABq, J = 9.78 Hz), 4.37 (1H, 1/2 ABq, J = 9.78 Hz), 4.55 (1H, dd, J = 9.69 Hz, J = 4.62 Hz), 4.90 (1H, 1/2 ABq, J = 12.71 Hz), 4.99 (1H, 1/2 ABq, J = 12.75 Hz), 5.13 (1H, 1/2 ABq, J = 12.33 Hz), 5.19 (1H, d, J = 3.32 Hz), 5.22 (1H, 1/2 ABq, J = 12.25 Hz), 5.66 (1H, d, J = 3.48 Hz), 6.08 (1H,

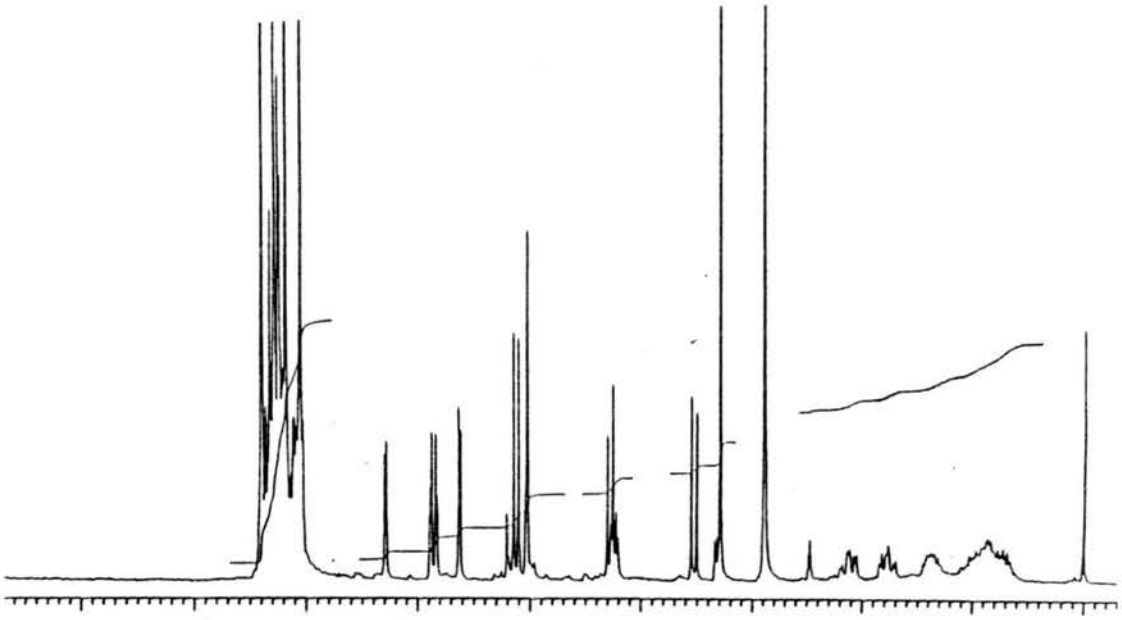
d, J = 3.03 Hz), 6.35 (1H, d, J = 3.45 Hz), 6.50-6.54 (2H, m), 7.01-7.34 (28H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1}; mp 99-101 °C; $[\alpha]^{25}_D$ -16° (c 0.5, CH_2Cl_2). Exact mass (FAB) calcd. for $C_{53}H_{50}N_2O_9Li$: 865.367637; found: 865.3675.



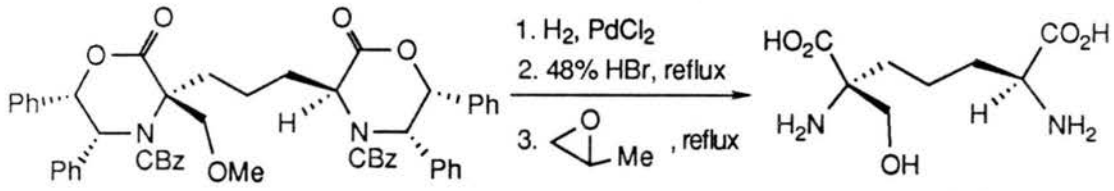
^1H NMR of **259a** in DMSO-d_6 at 393 °K

259b:

^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.64-1.02 (3H, m), 1.31-1.46 (1H, m), 1.70-1.85 (1H, m), 2.06-2.21 (1H, m), 3.29 (3H, s), 3.52 (1H, 1/2 ABq, J = 9.77 Hz), 4.24 (1H, dd, J = 9.66 Hz, J = 4.33 Hz), 4.27 (1H, 1/2 ABq, J = 9.83 Hz), 5.02 (2H, s), 5.07 (1H, 1/2 ABq, J = 12.74 Hz), 5.18 (1H, 1/2 ABq, J = 12.34 Hz), 5.62 (1H, d, J = 3.54 Hz), 5.83 (1H, d, J = 2.76 Hz), 5.88 (1H, d, J = 2.76 Hz), 6.29 (1H, d, J = 3.48 Hz), 7.03-7.43 (30H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1}; mp 114-116 °C; $[\alpha]^{25}_D$ -20.6° (c 0.6, CH_2Cl_2). Exact mass (FAB) calcd. for $C_{53}H_{50}N_2O_9Li$: 865.367637; found: 865.3662.



^{1}H NMR of **259b** in DMSO-d_6 at 393 °K

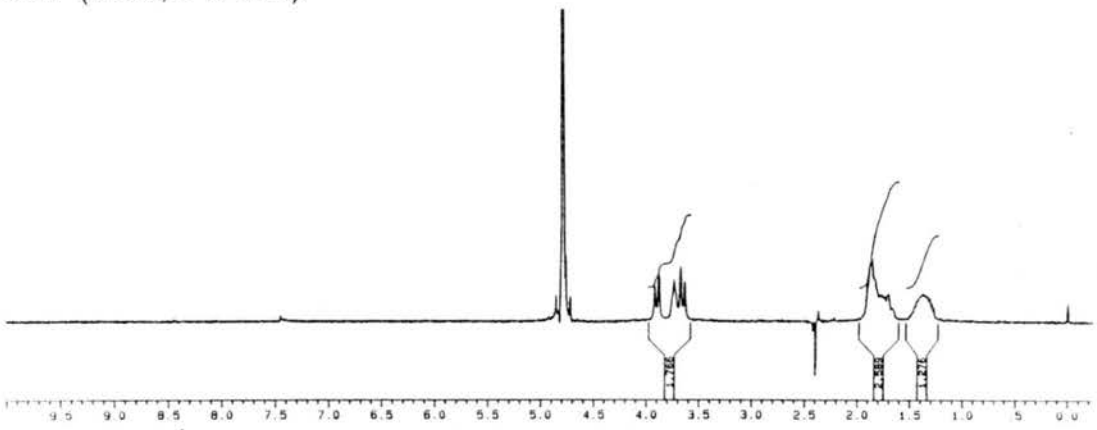


259a **256**

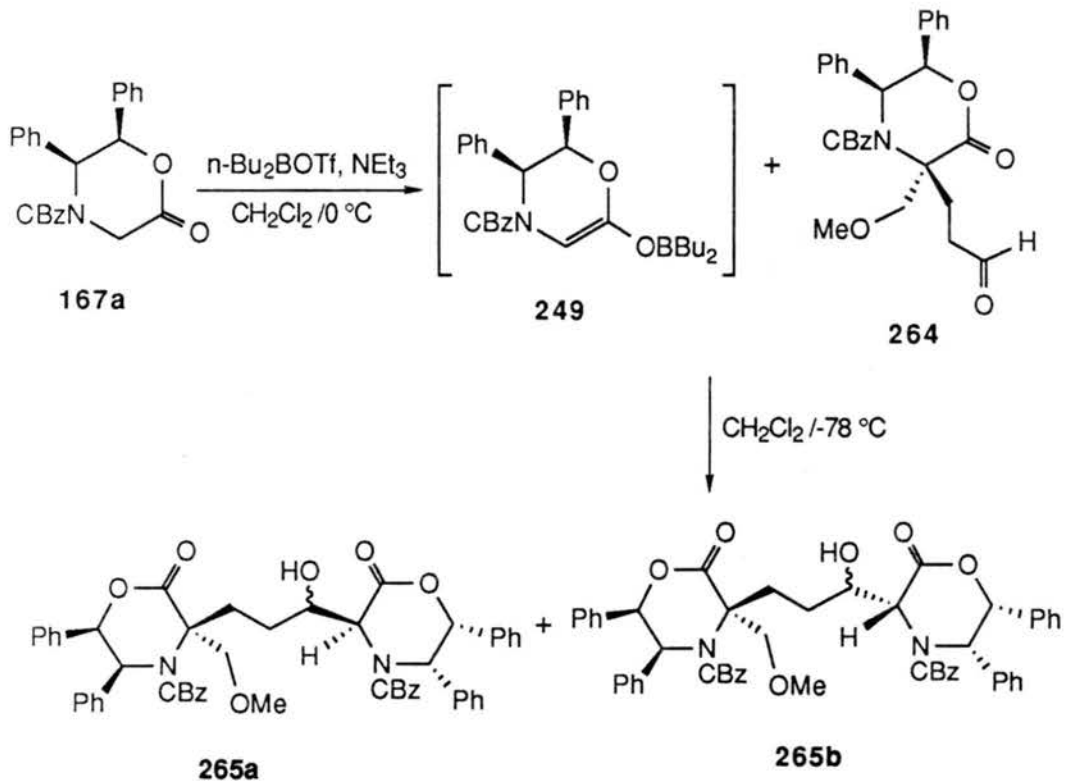
(2S,6R)-2,6-Diamino-6-hydroxymethylpimelic acid (256)

To a solution of **259a** (66 mg, 0.077 mmol, 1 equiv) in THF and EtOH (3ml, 1:1) was added palladium chloride (41 mg, 0.231 mmol, 3 equiv). The reaction mixture was hydrogenated at 50 psi for 48 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo line. The crude product was dissolved in 48% HBr and refluxed for 3 hr. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 16 mg (95%) of **256** as white solid.

^{1}H NMR (300 MHz, D_2O, vs DSS) δ 1.26-1.45 (2H, m), 1.65-1.90 (4H, m), 3.66 (1H, 1/2 ABq, J = 11.90 Hz), 3.74 (1H, m) 3.80 (1H, 1/2 ABq, J = 11.80 Hz); IR (ZnS, H_2O) 3435, 3119, 1618 cm^{-1}; mp 220-230 °C (decom.); $[\alpha]^{25}_D$ +22.5° (c 0.6, 5 N HCl).



^{1}H NMR of **256** in D_2O at 295 °K



167a **249** **264**

265a **265b**

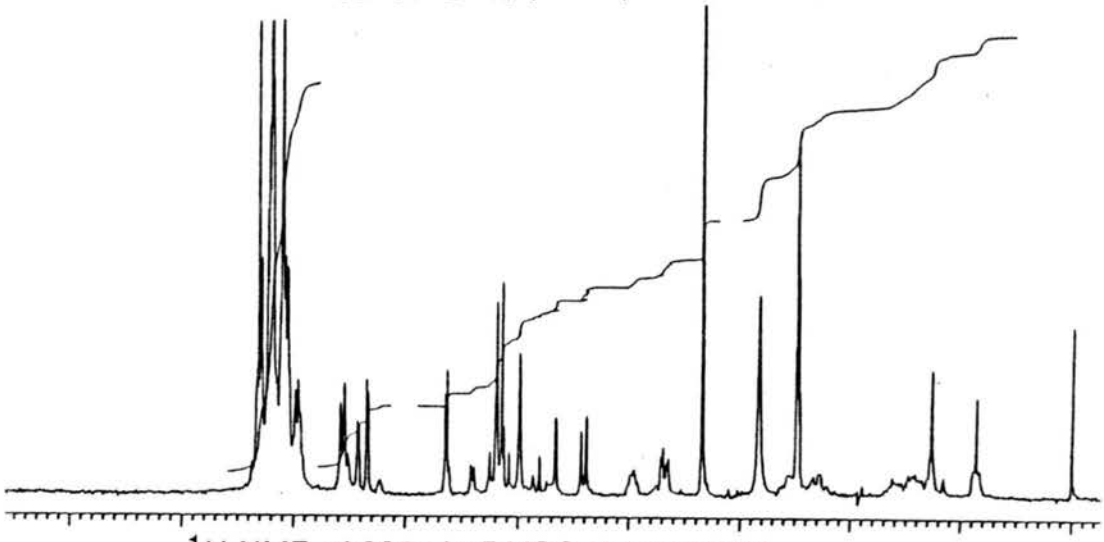
265a and 265b

To a solution of **167a** (407 mg, 1.05 mmol, 1 equiv) in CH_2Cl_2 (8 ml) was added dibutylboron triflate (2.1 ml, 2.1 mmol, 2 equiv, 1 M solution in

CH_2Cl_2) followed by addition of triethylamine (293 µl, 2.1 mmol, 2 equiv) at 0 °C. After 20 min the reaction mixture was cooled down to -78 °C and a CH_2Cl_2 (10 ml) solution of **264** (1.024 gm, 2.1 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with phosphate buffer solution (pH = 6.9), poured into water. The aqueous layer was extracted 3 × with CH_2Cl_2. The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 465 mg (50.6%) of **265a** as white solid and 17 mg (2%) of **265b** as white solid.

265a:

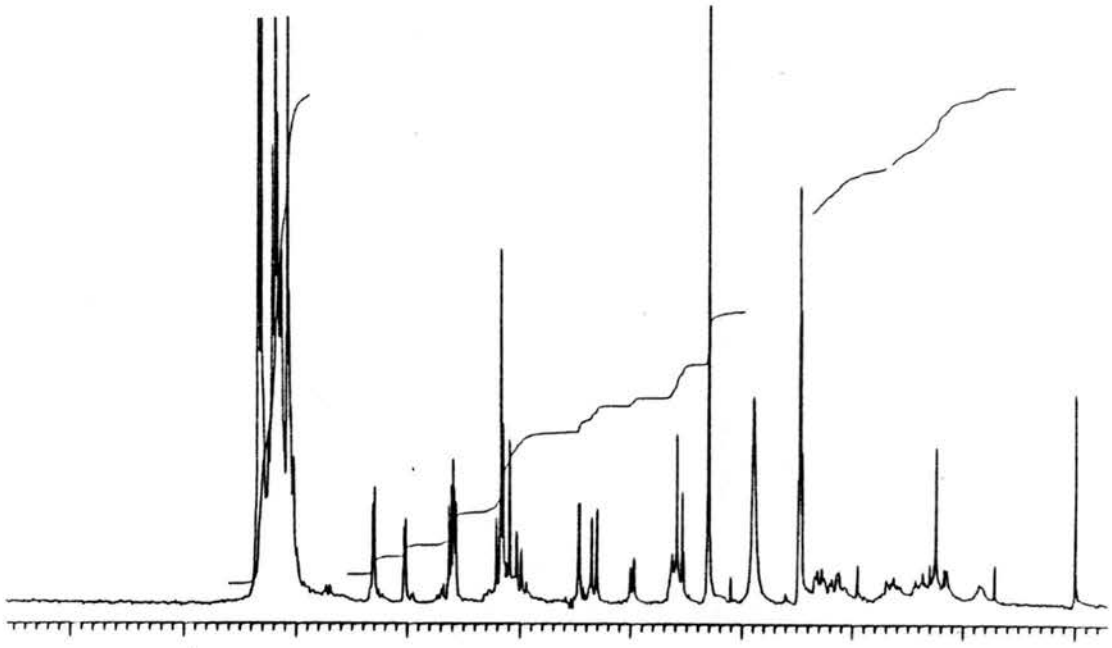
^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.34-1.69 (2H, m), 2.19-2.64 (2H, m), 3.34 (3H, s), 3.64-3.71 (1H, m), 3.91-4.02 (1H, m), 4.40 (1H, 1/2 ABq, J = 9.87 Hz), 4.66 (1H, s), 4.98 (2H, s), 5.11 (1H, 1/2 ABq, J = 12.38 Hz), 5.13 (1H, d, J = 3.16 Hz), 5.22 (1H, 1/2 ABq, J = 12.58 Hz), 5.40 (1H, d, D_2O exch., J = 5.22 Hz), 5.64 (1H, d, J = 3.64 Hz), 6.34 (1H, d, J = 3.43 Hz), 6.42 (1H, d, J = 3.04 Hz), 6.55-6.58 (2H, m), 6.91-7.37 (28H, m); IR (NaCl, CH_2Cl_2) 3477, 1749, 1704 cm^{-1}; mp 92-94 °C; $[\alpha]^{25}D$ +3.6° (c 0.94, CH_2Cl_2). Exact mass calcd. for $C_{53}H_{51}N_2O_{10}$ (M^++H): 875.35453; found: 875.3508.



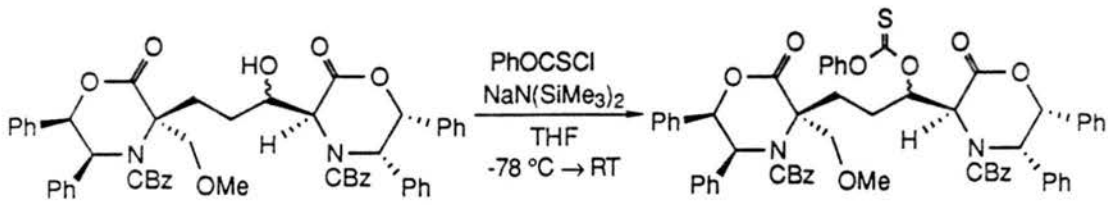
^1H NMR of **265a** in DMSO-d_6 at 393 °K

265b:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.27-1.45 (1H, m), 1.58-1.76 (1H, m), 2.05-2.41 (2H, m), 3.31 (3H, s), 3.56 (1H, 1/2 ABq, J = 9.70 Hz), 3.52-3.63 (1H, m), 3.99 (1H, d, D_2O exch., J = 6.70 Hz), 4.33 (1H, 1/2 ABq, J = 9.75 Hz), 4.47 (1H, d, J = 2.39 Hz), 5.06 (1H, 1/2 ABq, J = 12.64 Hz), 5.17 (2H, s), 5.18 (1H, 1/2 ABq, J = 12.22 Hz), 5.57 (1H, d, J = 3.49 Hz), 5.60 (1H, d, J = 3.60 Hz), 6.02 (1H, d, J = 3.45 Hz), 6.30 (1H, d, J = 3.47 Hz), 7.02-7.33 (30H, m); IR (NaCl, CH_2Cl_2) 3488, 1747, 1704 cm^{-1}; mp 105-107 °C; $[\alpha]^{25}_D$ +56.9° (c 0.36, CH_2Cl_2).



^{1}H NMR of **265b** in DMSO-d_6 at 393 °K

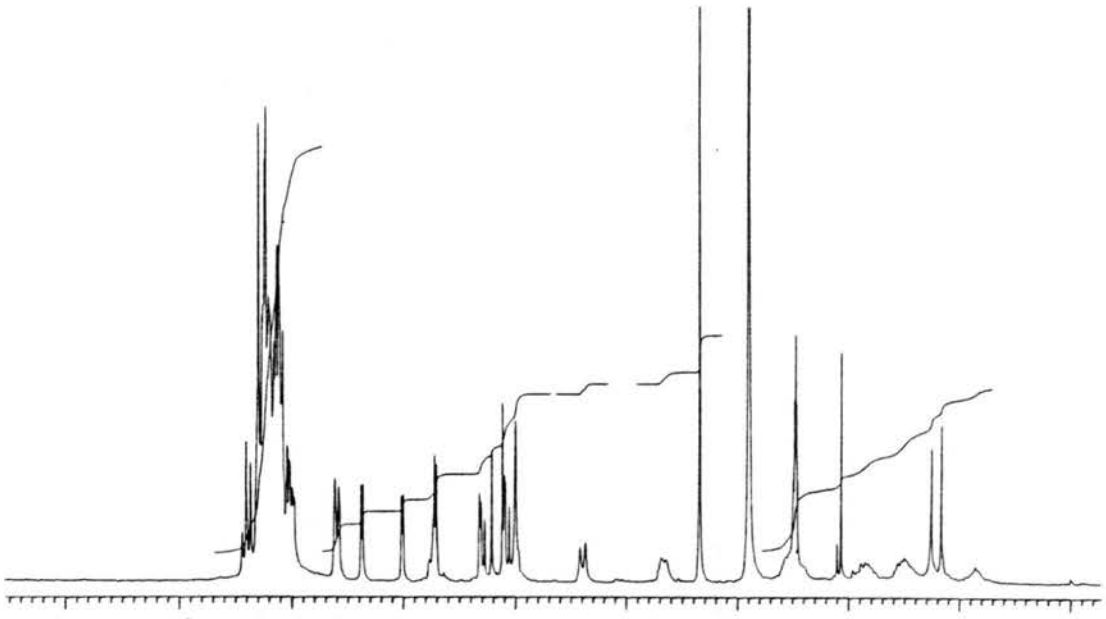


265a **266**

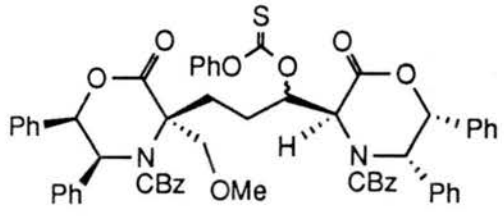
266

To a solution of **265a** (400 mg, 0.457 mmol, 1 equiv) in THF (4ml) was added phenyl chlorothionoformate (316 µl, 2.284 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (503 µl, 0.503 mmol, 1.1 equiv, 1 M solution in THF) at -78 °C. After 3 hr, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 174 mg (38%) of **266** as white solid and 135 mg (34%) of unreacted 1.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.41-1.59 (1H, m), 1.76-1.95 (1H, m), 2.36-2.61 (2H, m), 3.35 (3H, s), 3.66 (1H, 1/2 ABq, J = 9.77 Hz), 4.39 (1H, 1/2 ABq, J = 9.70 Hz), 5.00 (2H, s), 5.08 (1H, 1/2 ABq, J = 12.32 Hz), 5.09 (1H, d, J = 1.70 Hz), 5.24 (1H, 1/2 ABq, J = 12.44 Hz), 5.31 (1H, d, J = 3.15 Hz), 5.71 (1H, d, J = 3.54 Hz), 5.73 (1H, m), 6.01 (1H, d, J = 3.09 Hz), 6.37 (1H, d, J = 3.40 Hz), 6.60 (2H, d, J = 6.74 Hz), 6.98-7.44 (33H, m); IR (NaCl, CH_2Cl_2) 1748, 1705 cm^{-1};

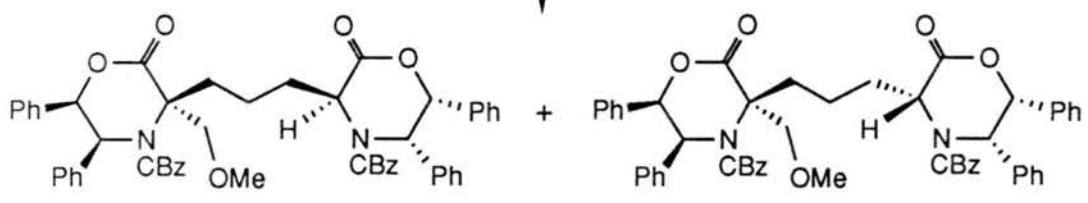


^{1}H NMR of **266** in DMSO-d_6 at 393 °K



266

n-Bu_3SnH, AIBN
toluene /reflux



267a + **267b**

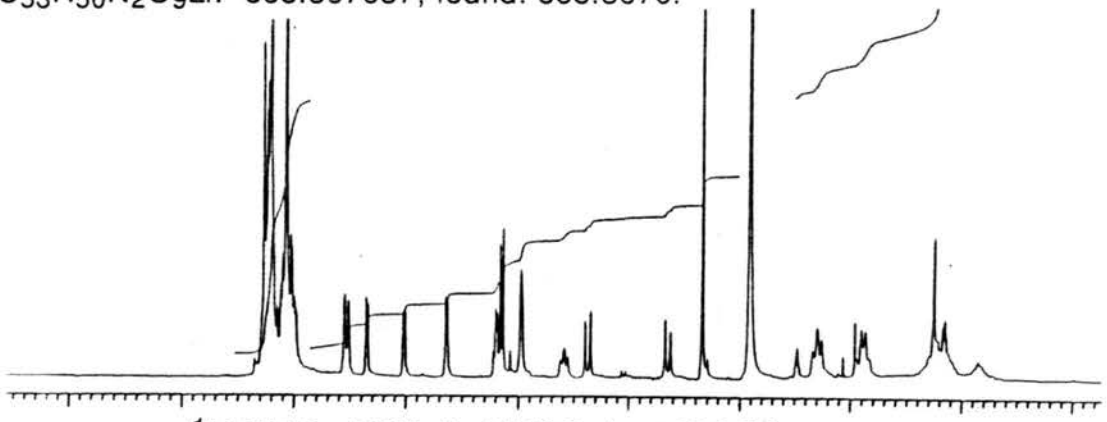
267a and 267b

To a solution of **266** (155 mg, 0.153 mmol, 1 equiv) in toluene was added AIBN (8 mg, 0.049 mmol, 0.3 equiv) followed by addition of triphenyltin hydride (269 mg, 0.766 mmol, 5 equiv). The resulting solution was brought to

reflux. After 2.5 hr touene was evaporated off and the residue was separated in column chromatography on silica gel to afford 107 mg (81%) of **267a** as white solid and 7 mg (5.3%) of **267b** as white solid.

267a:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.09-1.32 (2H, m), 1.88 (2H, q, J = 7.67 Hz), 2.30 (2H, t, J = 8.07 Hz), 2.91 (3H, s), 3.65 (1H, 1/2 ABq, J = 9.87 Hz), 4.37 (1H, 1/2 ABq, J = 9.78 Hz), 4.58 (1H, t, J = 6.43 Hz), 4.98 (2H, s), 5.10 (1H, 1/2 ABq, J = 12.31 Hz), 5.19 (1H, d, J = 2.99 Hz), 5.20 (1H, 1/2 ABq, J = 12.42 Hz), 5.63 (1H, d, J = 3.36 Hz), 6.01 (1H, d, J = 3.02 Hz), 6.35 (1H, d, J = 3.40 Hz), 6.51-6.55 (2H, m), 6.98-7.29 (28H, m); IR (NaCl, CH_2Cl_2) 1750, 1705 cm^{-1}; mp 98-100 °C; $[\alpha]^{25}_D$ -8.8° (c 0.5, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{53}H_{50}N_2O_9$: C, 74.11; H, 5.87; N, 3.26. Found: C, 74.18; H, 6.04; N, 3.08. Exact mass (FAB) calcd. for $C_{53}H_{50}N_2O_9Li$: 865.367637; found: 865.3670.

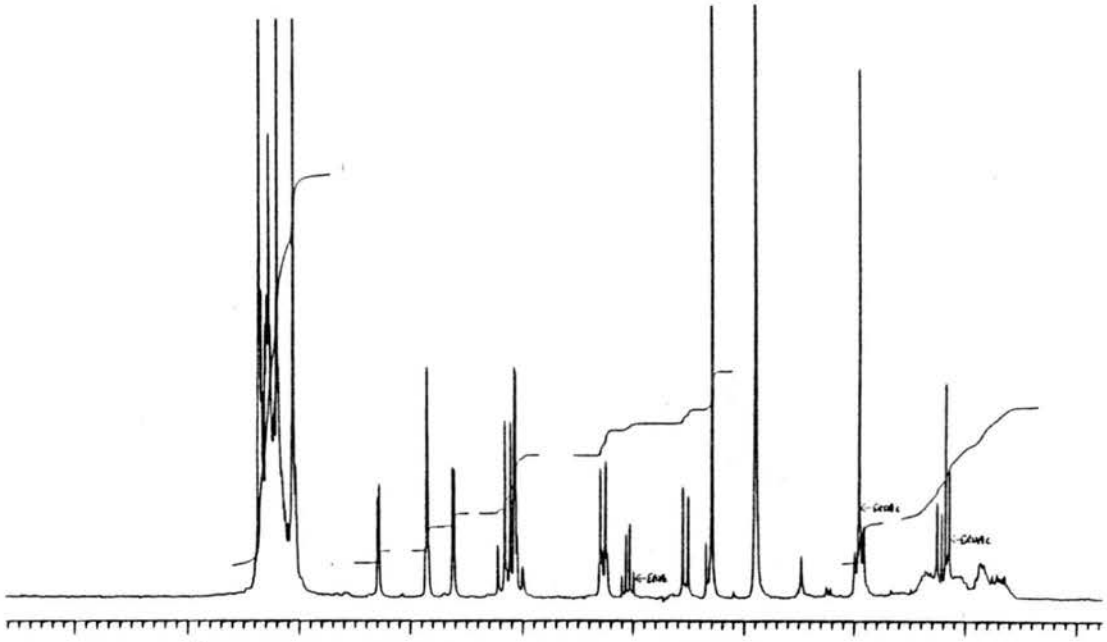


^{1}H NMR of **267a** in DMSO-d_6 at 393 °K

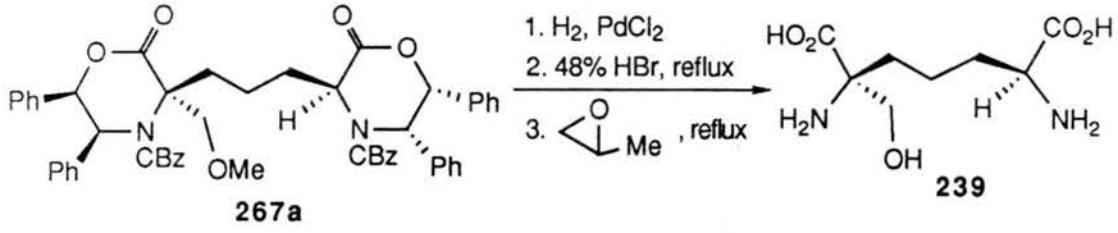
267b:

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.66-0.89 (2H, m), 1.01-1.14 (1H, m), 1.28-1.42 (1H, m), 1.96 (2H, t, J = 8.28 Hz), 3.30 (3H, s), 3.53 (1H, 1/2 ABq, J = 9.75 Hz), 4.25 (1H, t, J = 4.61 Hz), 4.27 (1H, 1/2 ABq, J = 9.72 Hz), 5.02 (1H, 1/2 ABq, J = 12.87 Hz), 5.08 (1H, 1/2 ABq, J = 12.51 Hz), 5.11 (1H, 1/2 ABq, J = 12.86 Hz), 5.19 (1H, 1/2 ABq, J = 12.58 Hz), 5.61 (1H, d,

J = 3.56 Hz), 5.84 (1H, d, J = 3.29 Hz), 5.86 (1H, d, J = 3.32 Hz), 6.29 (1H, d, J = 3.49 Hz), 7.01-7.39 (30H, m); IR (NaCl, CH_2Cl_2) 1749, 1705 cm^{-1}; mp 88-90 °C; $[\alpha]^{25}_D$ +12.9° (c 0.22, CH_2Cl_2).



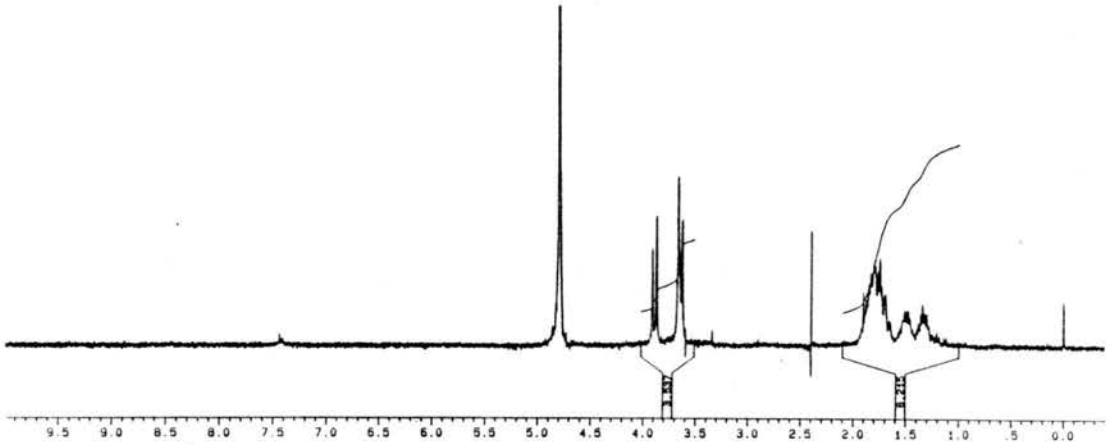
^1H NMR of **267b** in DMSO-d_6 at 393 °K



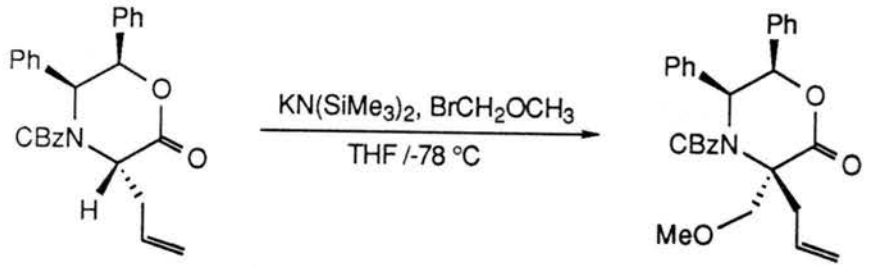
(2S,6S)-2,6-Diamino-6-hydroxymethylpimelic acid (239)

To a solution of **267a** (73 mg, 0.085 mmol, 1 equiv) in THF and EtOH (3ml, 1:1) was added palladium chloride (90 mg, 0.508 mmol, 6 equiv). The reaction mixture was hydrogenated at 50 psi for 48 hr. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo line. The crude product was dissolved in 48% HBr and refluxed for 3 h. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 17 mg (91%) of **239** as white solid.

^{1}H NMR (300 MHz, D_2O, vs DSS) δ 1.29-1.39 (1H, m), 1.43-1.57 (1H, m), 1.62-1.90 (4H, m) 3.64 (1H, 1/2 ABq, J = 11.69 Hz), 3.65 (1H, m), 3.89 (1H, 1/2 ABq, J = 11.83 Hz); IR (ZnS, H_2O) 3395, 3109, 1614 cm^{-1}; mp 235-245 °C (decom.), Lit.[65] 240-250 °C (decom.); $[\alpha]^{25}_D$ +7.1° (c 0.55, 5 N HCl), Lit.[65] +8.1±1.0° (c 0.506, 5 N HCl).



^{1}H NMR of **239** in D_2O at 295 °K



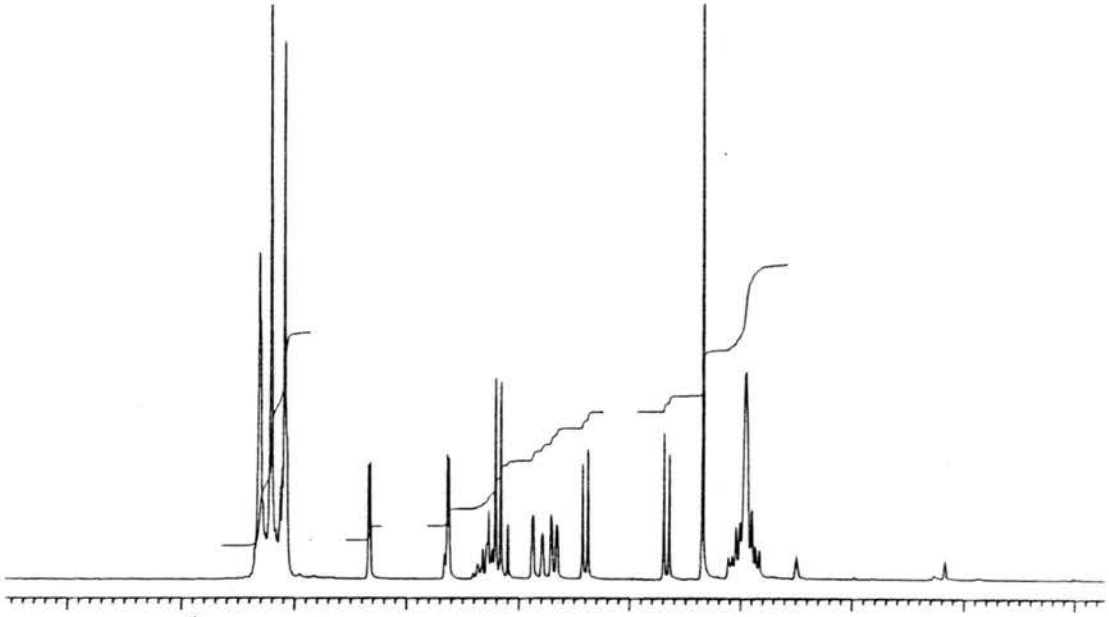
209 **270**

(D,L)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methoxymethyl-3-(2'-propenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (270)

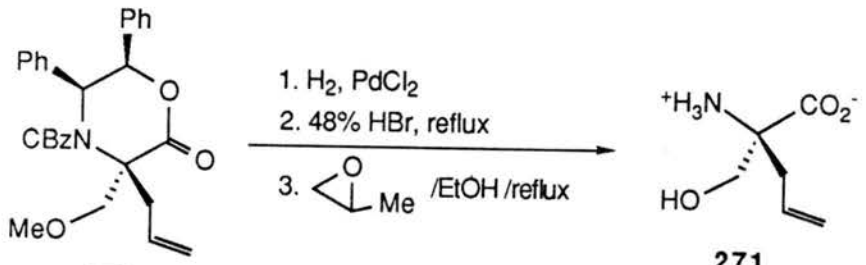
To a stirred solution of **209** (699 mg, 1.635 mmol, 1 equiv) in THF (10 ml) was added potassium bis(trimethylsilyl)amide (3.5 ml, 4.9 mmol, 3 equiv, 1.4 M solution in THF) dropwise via syringe at -78 °C. After 5 min bromomethyl methyl ether (667 µl, 8.171 mmol, 5 equiv) was added to the reaction mixture at -78 °C. After further 50 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over

anhydrous magnesium sulfate, filtered, concentrated and separated in column chromatography on silica gel to afford 573 mg (74%) of **270** as colorless oil.

^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.82-3.11 (2H, m), 3.34 (3H, s), 3.66 (1H, 1/2 ABq, J = 9.82 Hz), 4.40 (1H, 1/2 ABq, J = 9.83 Hz), 4.77-4.88 (2H, m), 5.12 (1H, 1/2 ABq, J = 12.34 Hz), 5.15-5.41 (1H, m), 5.23 (1H, 1/2 ABq, J = 12.46 Hz), 5.62 (1H, d, J = 3.43 Hz), 6.32 (1H, d, J = 3.42 Hz), 7.06-7.30 (15H, m); IR (NaCl, CH_2Cl_2) 1748, 1703 cm^{-1}.



^{1}H NMR of **270** in DMSO-d_6 at 393 °K



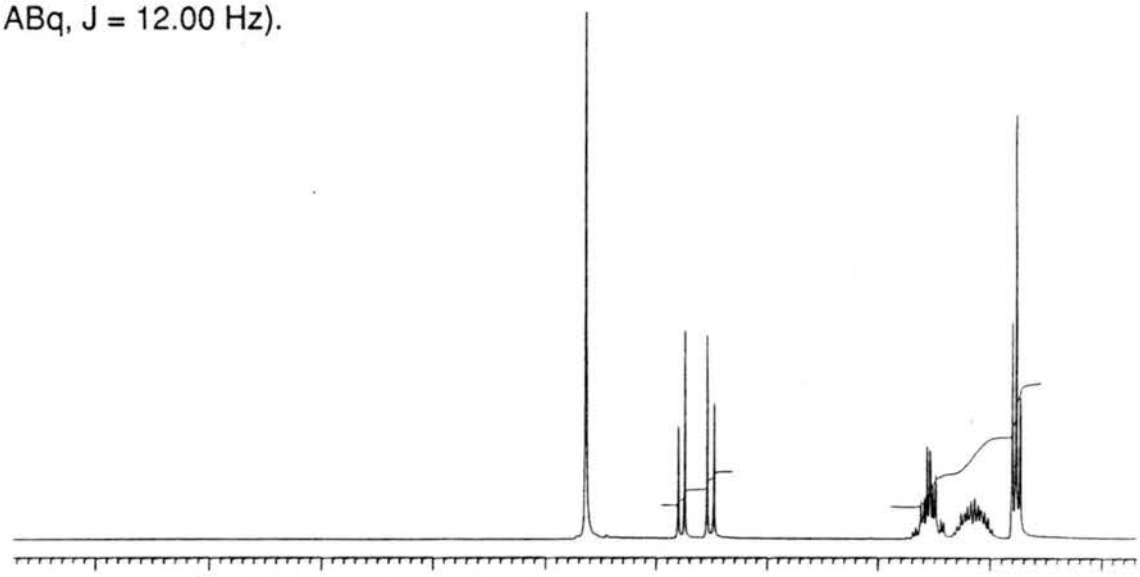
270 **271**

(D,L)-2-Propylserine (271)

To a solution of **270** (573 mg, 1.215 mmol, 1 equiv) in THF and EtOH (6 ml, 1:1) was added palladium chloride (215 mg, 1.213 mmol, 1 equiv). The reaction mixture was hydrogenated at 50 psi for 24 hr. The mixture was then

purged with nitrogen, filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo line. The crude product was dissolved in 48% HBr and refluxed for 3 hr. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 215 mg (84%) of **271** as white solid.

^{1}H NMR (200 MHz, D_2O, vs HOD) δ 0.77 (3H, t, J = 7.40 Hz), 0.99-1.32 (2H, m), 1.41-1.69 (2H, m), 3.52 (1H, 1/2 ABq, J = 12.09 Hz), 3.77 (1H, 1/2 ABq, J = 12.00 Hz).



^{1}H NMR of **271** in D_2O at 295 °K

Determination of Optical Purity, General Procedure

The amino acids (5-10 mg) were converted into the corresponding ester hydrochloride as follows: All the α-monosubstituted amino acids except **199** were refluxed for 2 h in EtOH•HCl (2 ml, 1N) or MeOH•HCl (2 ml, 1N). The amino acid **199** labile to harsh acidic conditions were stirred for 3 h at ambient temperature in EtOH•HCl (2 ml, 1N). The α-disubstituted zwitterionic amino acids were refluxed for 4 hr in MeOH containing excess thionyl chloride. The N-t-BOC protected α-disubstituted amino acids were refluxed for 2 hr in H_2O•HCl (2 ml, 1 N), concentrated, dried in vacuo line and then the residue were refluxed for 4 hr in MeOH containing excess thionyl chloride.

The amino acid **216** followed the same procedure as the t-BOC protected α-disubstituted amino acids after hydrogenation of double bond. All the resulting reaction mixtures were cooled, concentrated, dried in vacuo line. The amino ester hydrochloride salts were treated with (+)- or (-)-α-methoxy-α-trifluoromethyl phenylacetyl chloride (1.2 equiv) in THF in the presence of excess propylene oxide at 50°C. After 1 hr, the solvent was evaporated and the residue was dried in vacuo line. The crude Mosher amides were analyzed by ^{1}H and ^{19}F NMR spectrums.

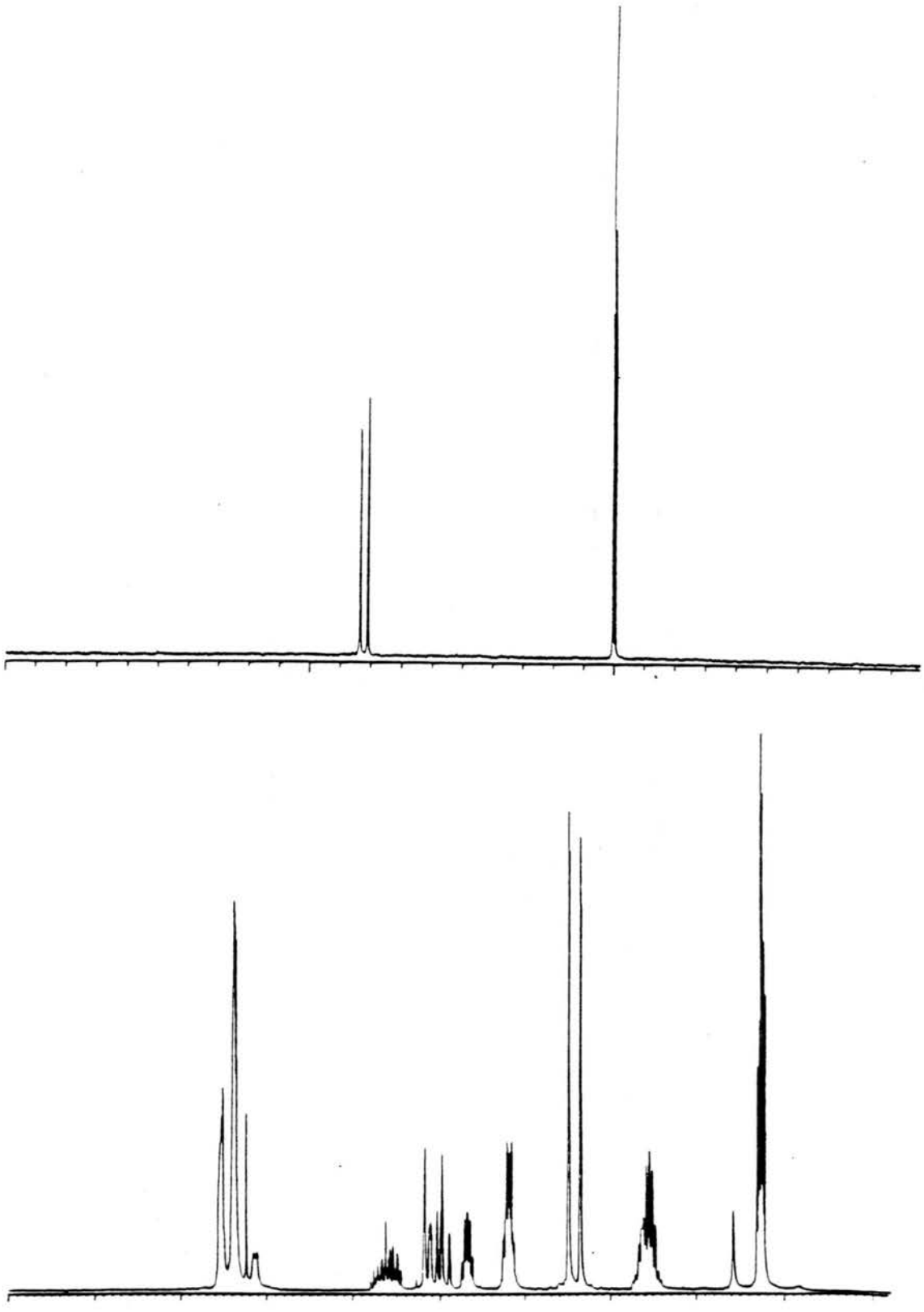


FIGURE 11a Racemic MPTA **193** ^{19}F and ^{1}H NMR

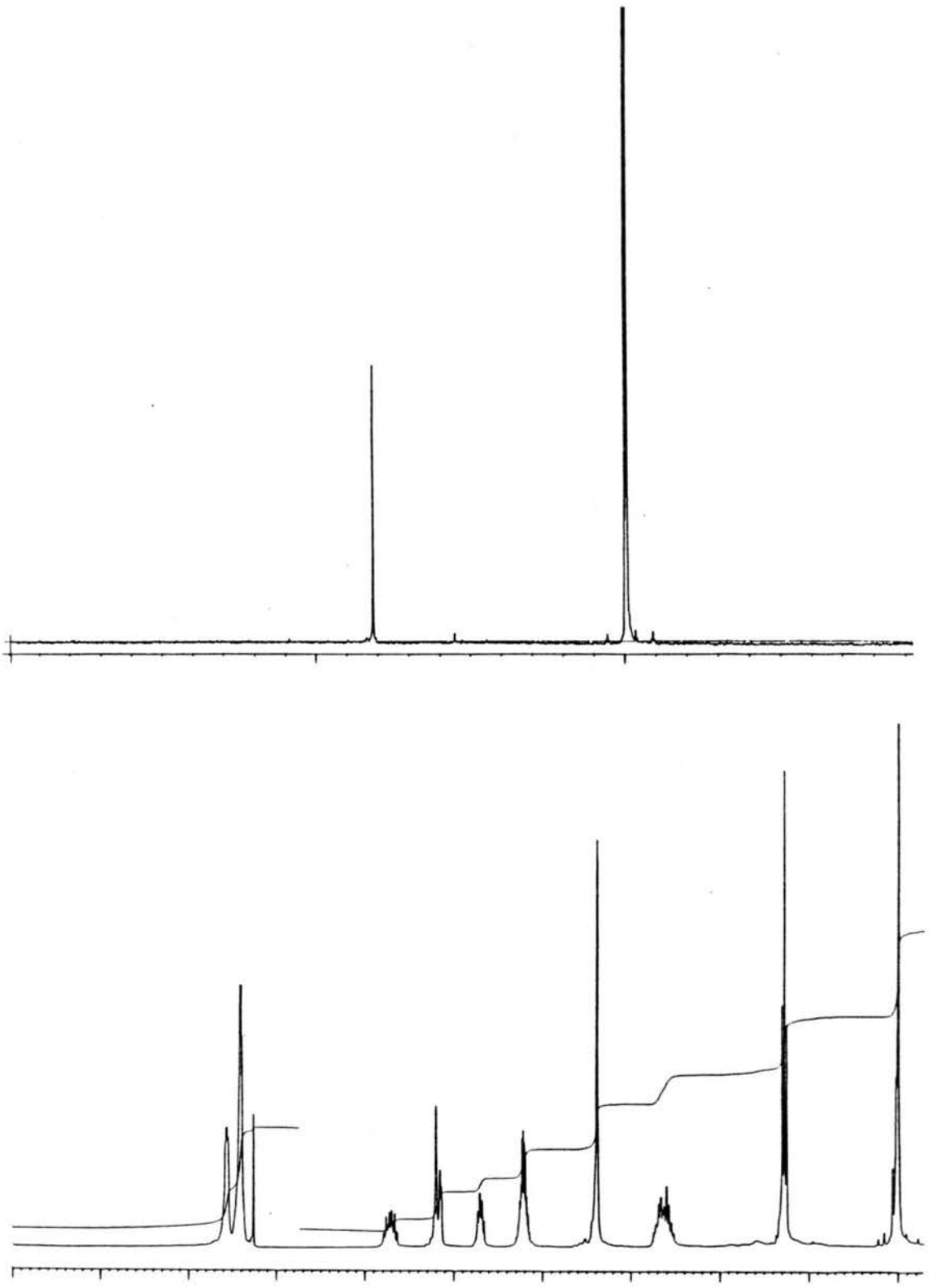


FIGURE 11b (+)-MPTA (Synthetic) **193** ^{19}F and ^{1}H NMR

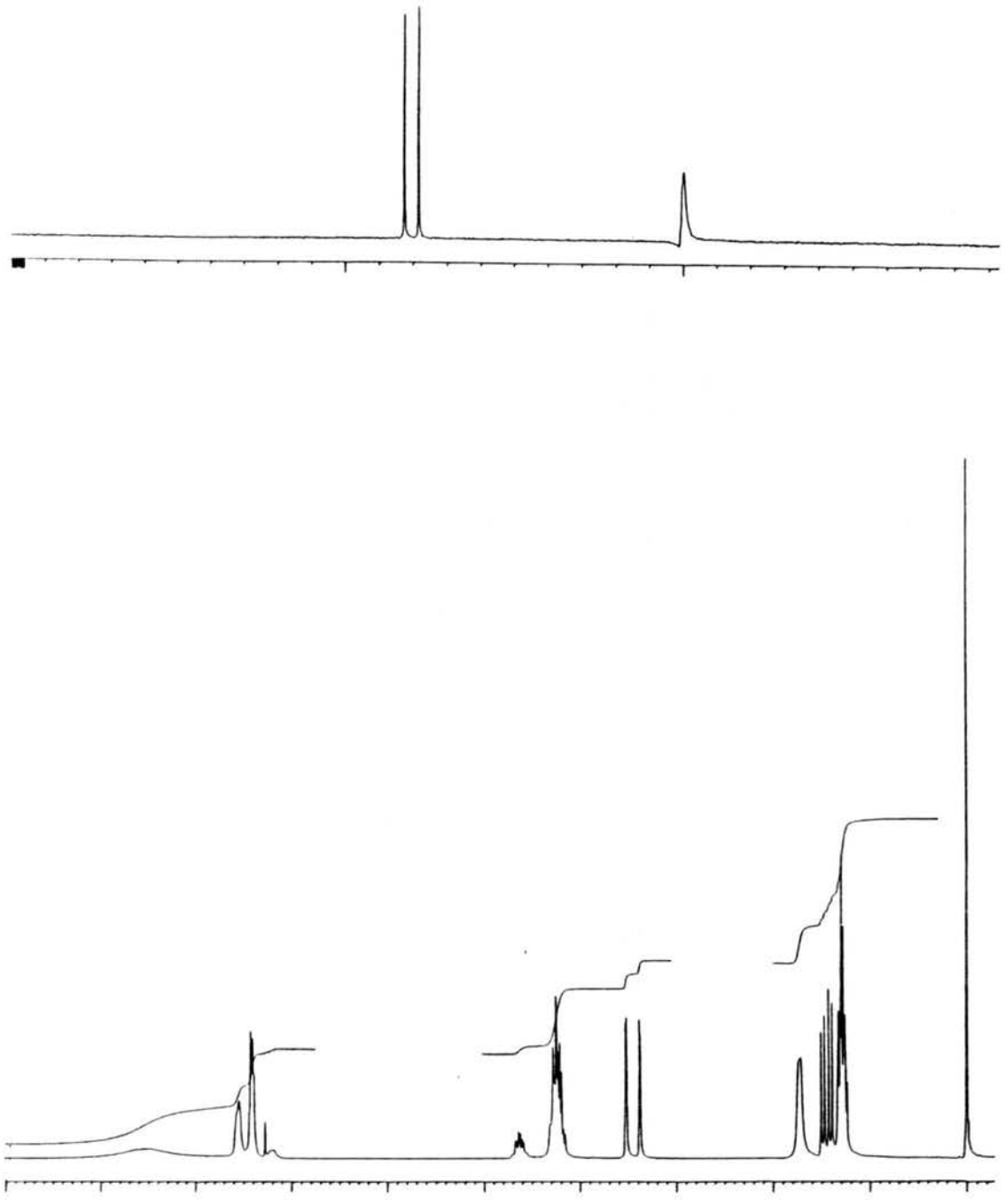


FIGURE 12a Racemic MPTA **194** ^{19}F and ^{1}H NMR

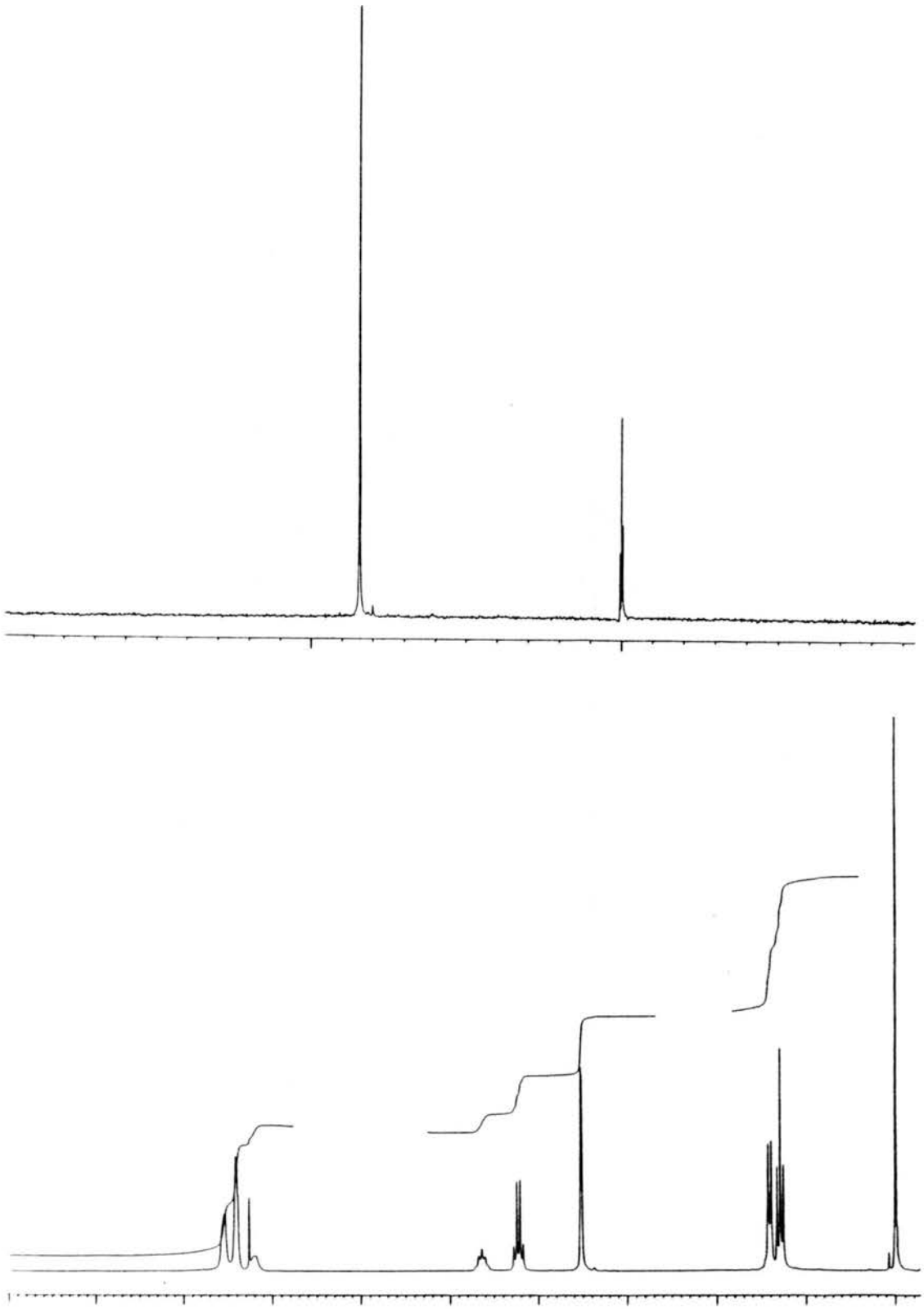


FIGURE 12b (-)-MPTA (Synthetic) **194** ^{19}F and ^{1}H NMR

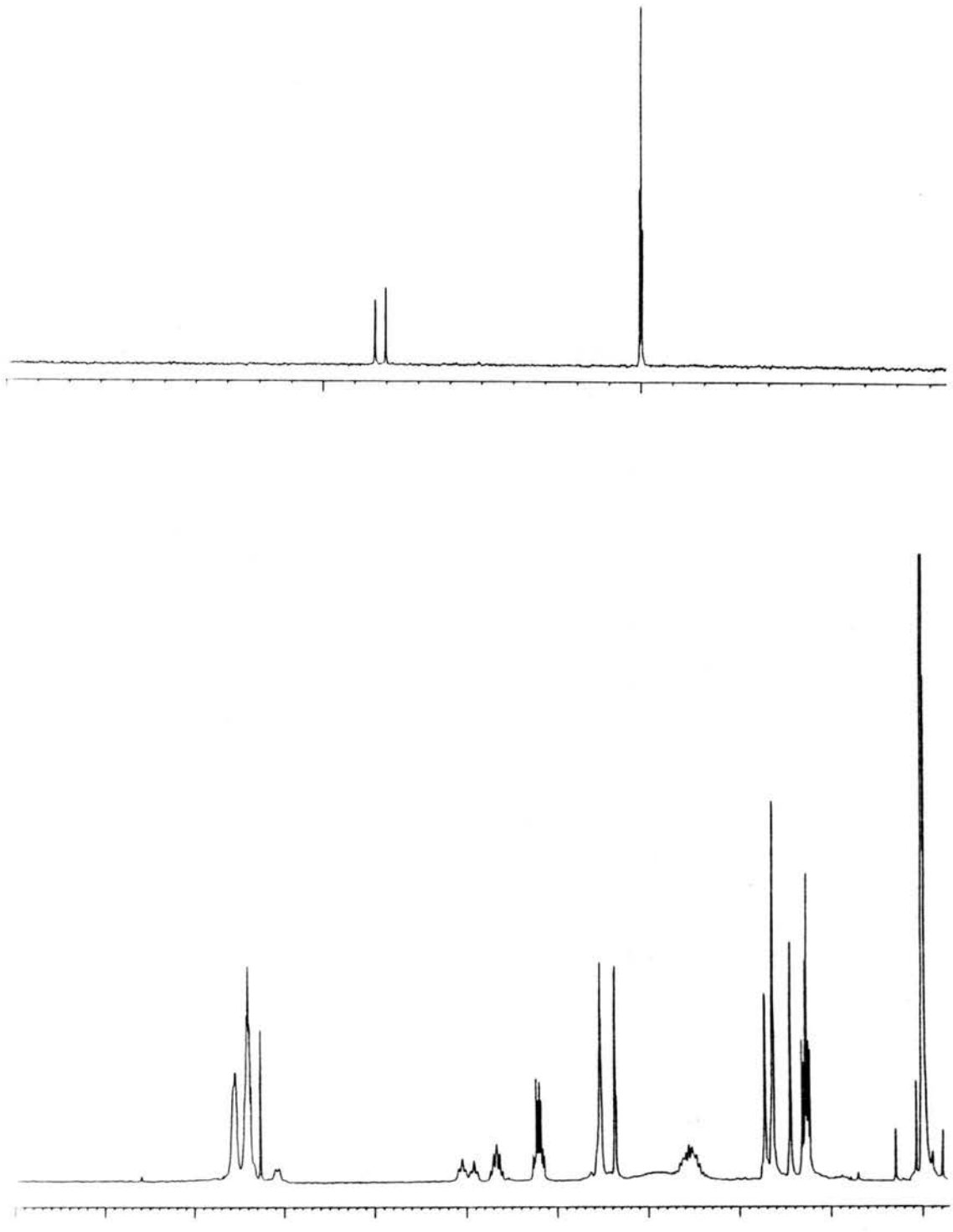


FIGURE 13a Racemic MPTA **201** ^{19}F and ^{1}H NMR

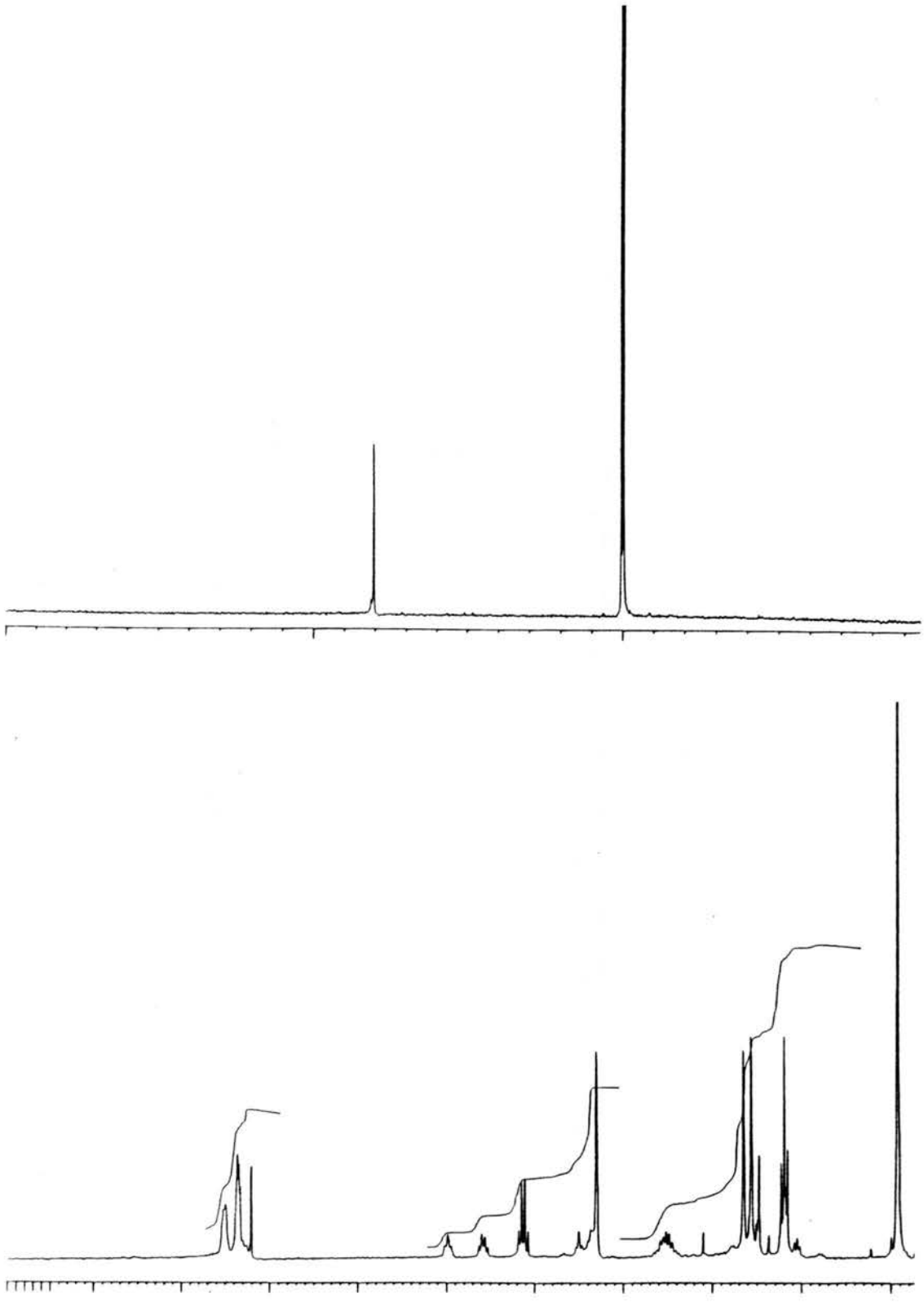


FIGURE 13b (+)-MPTA (Synthetic) **201** ^{19}F and ^{1}H NMR

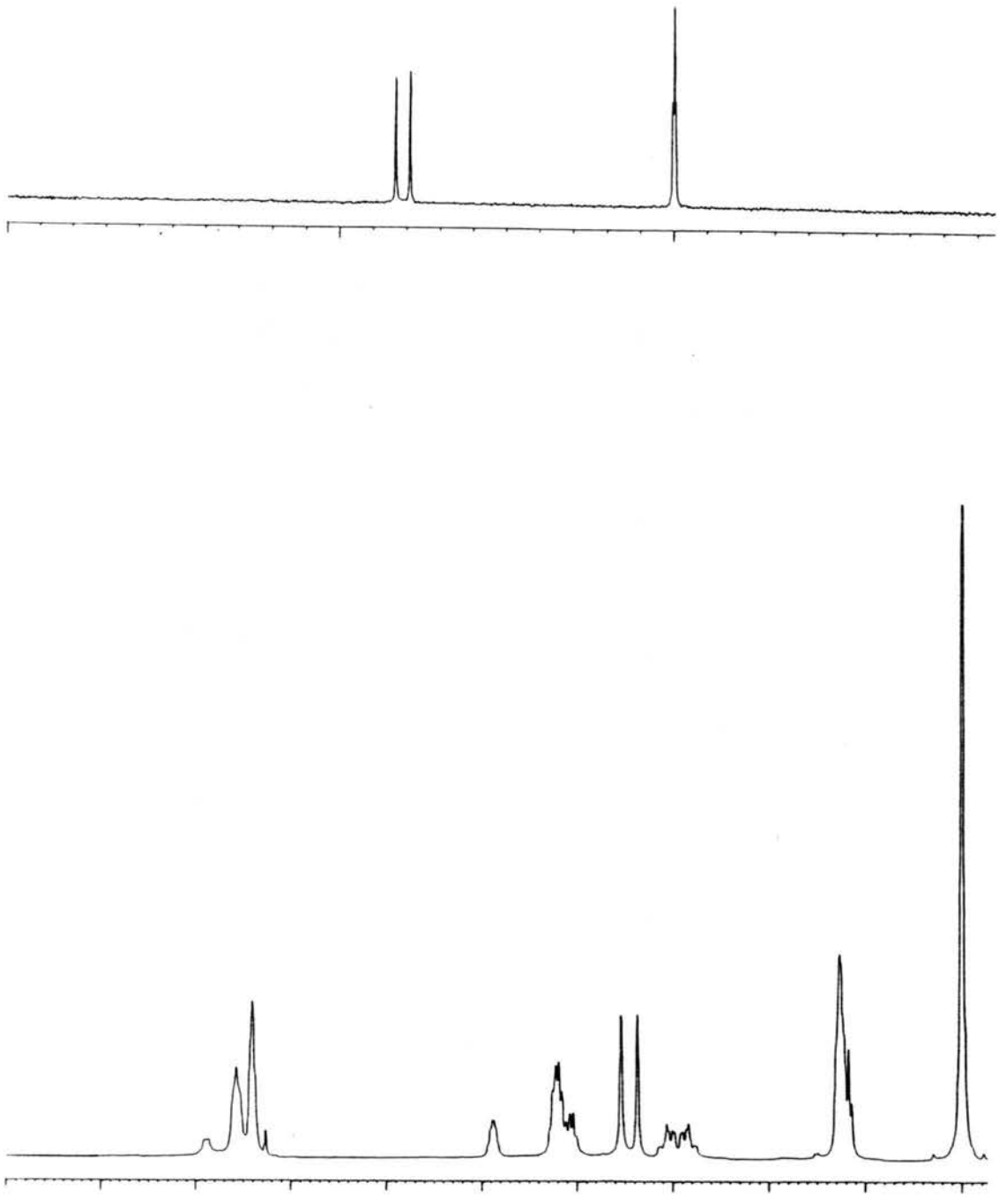


FIGURE 14a Racemic MPTA **205** ^{19}F and ^{1}H NMR

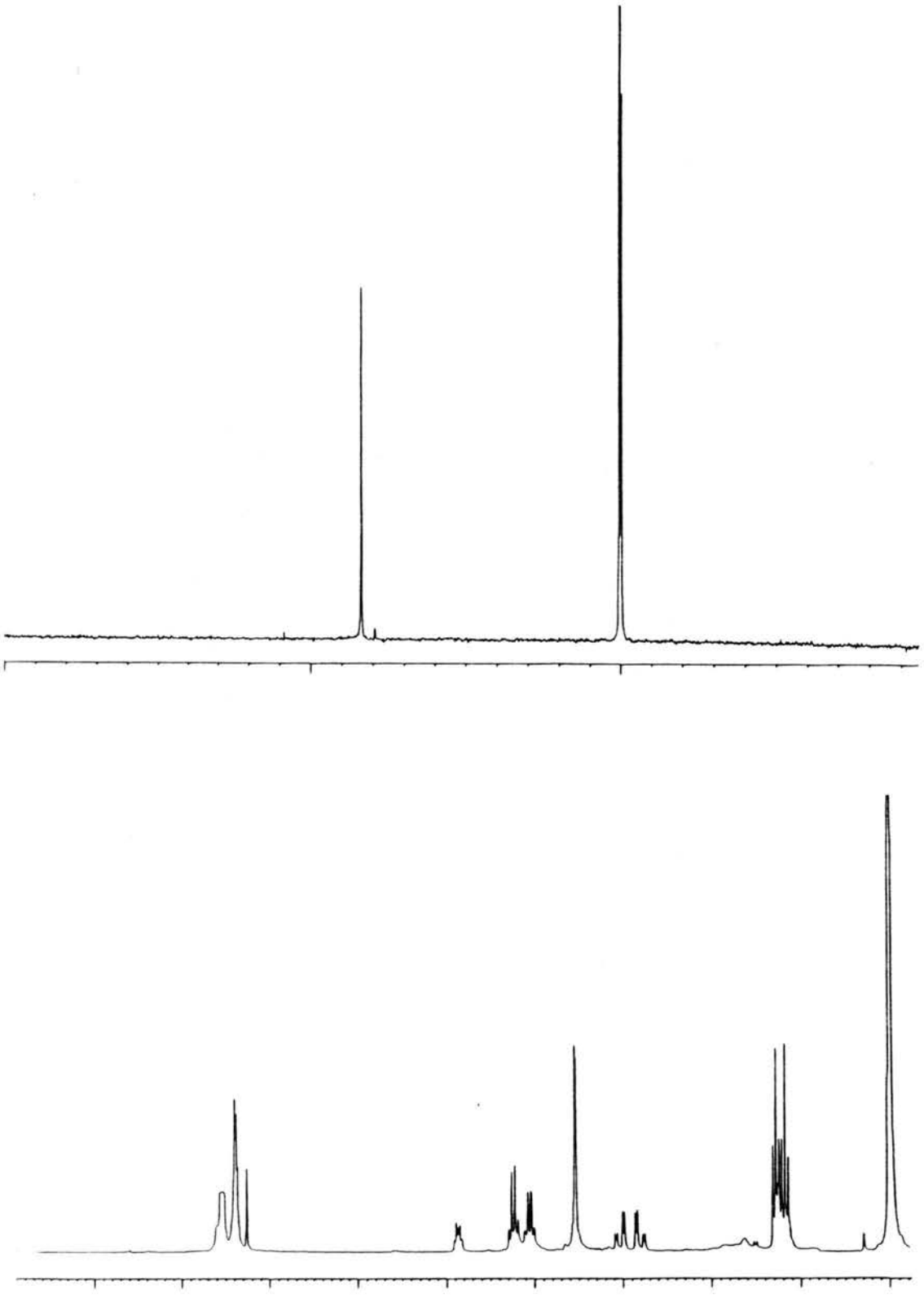


FIGURE 14b (+)-MPTA (Synthetic) **205** ^{19}F and ^{1}H NMR

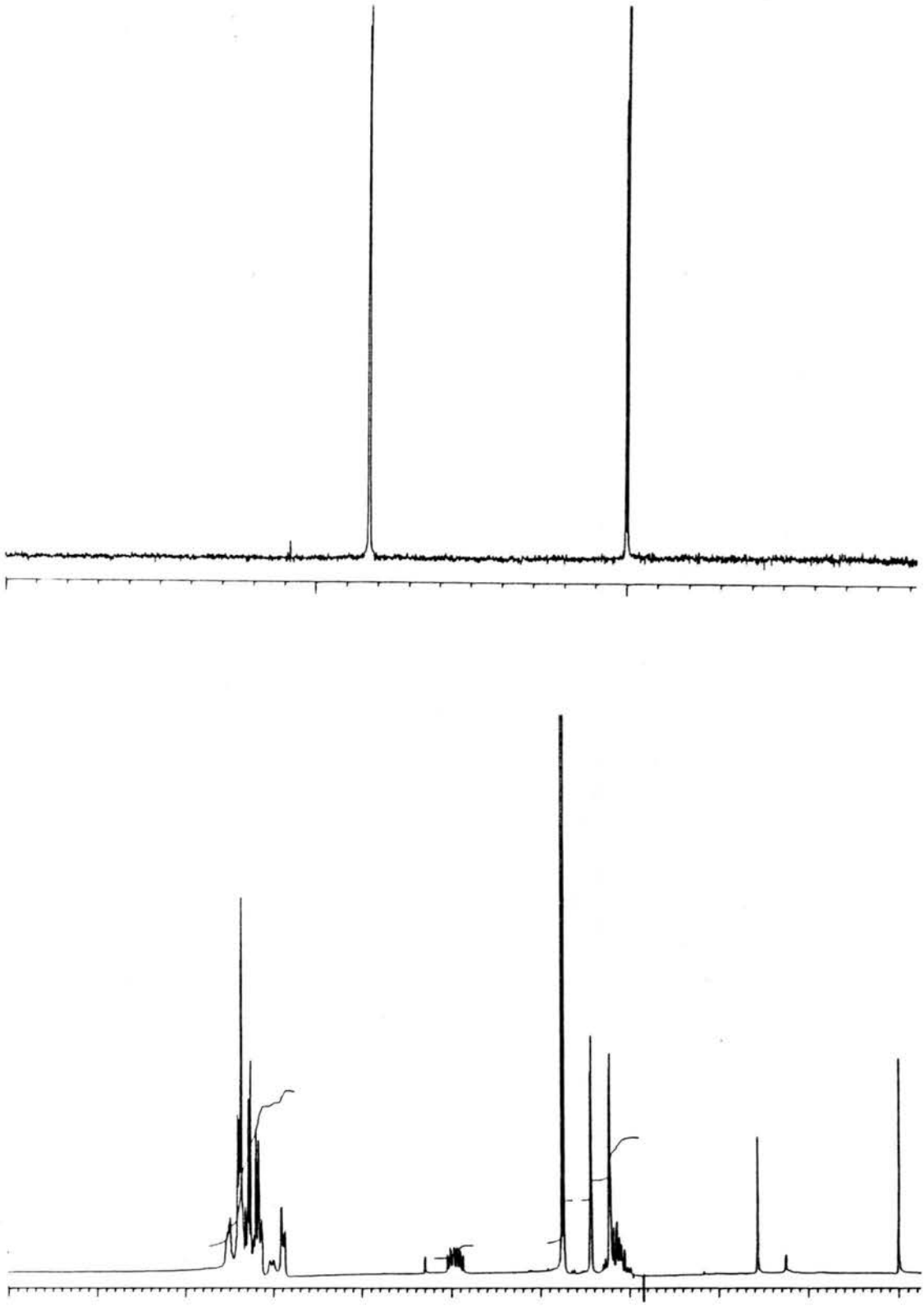


FIGURE 15a Racemic MPTA **211** ^{19}F and ^{1}H NMR

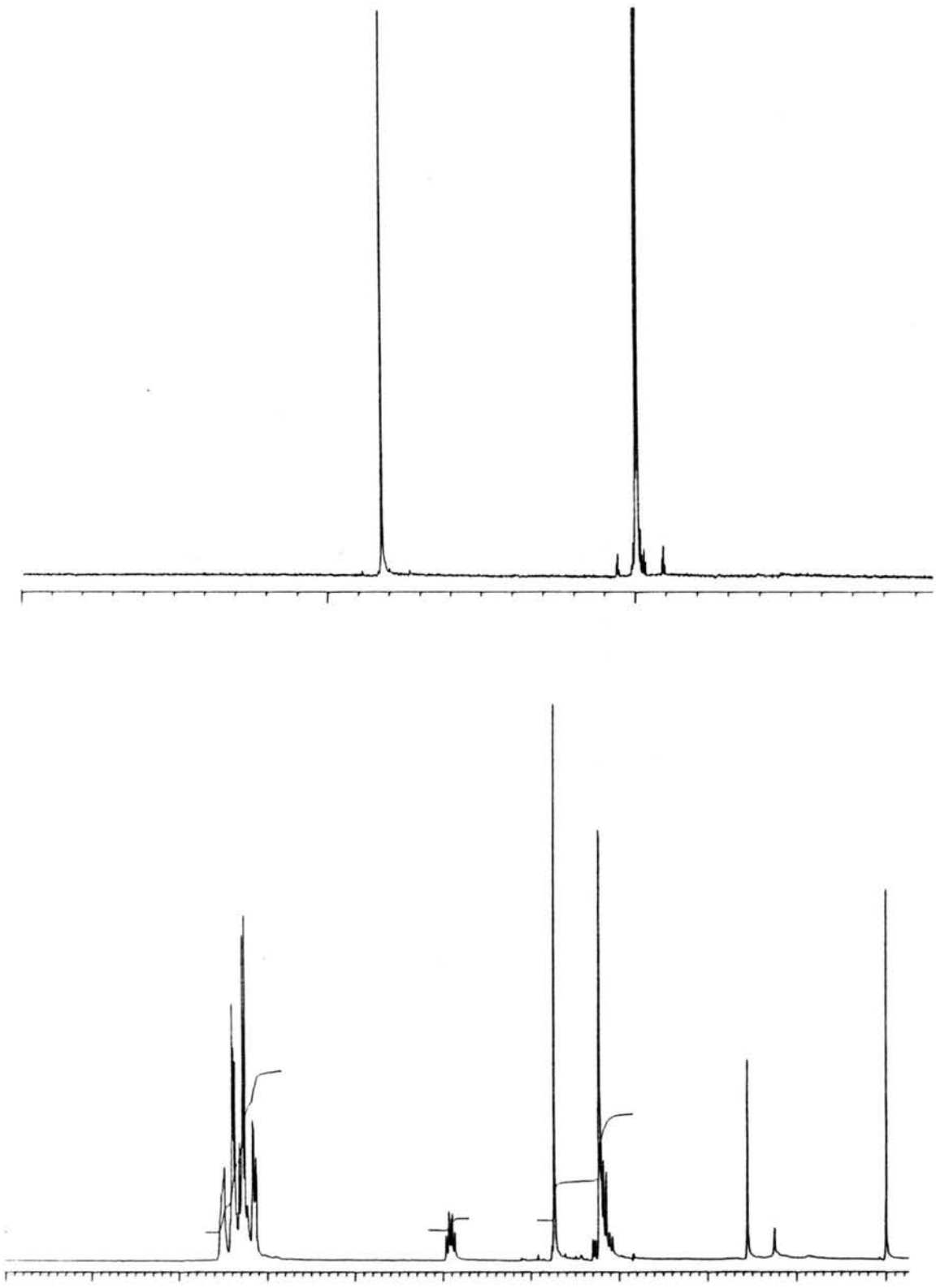


FIGURE 15b (-)-MPTA (Synthetic) **211** ^{19}F and ^{1}H NMR

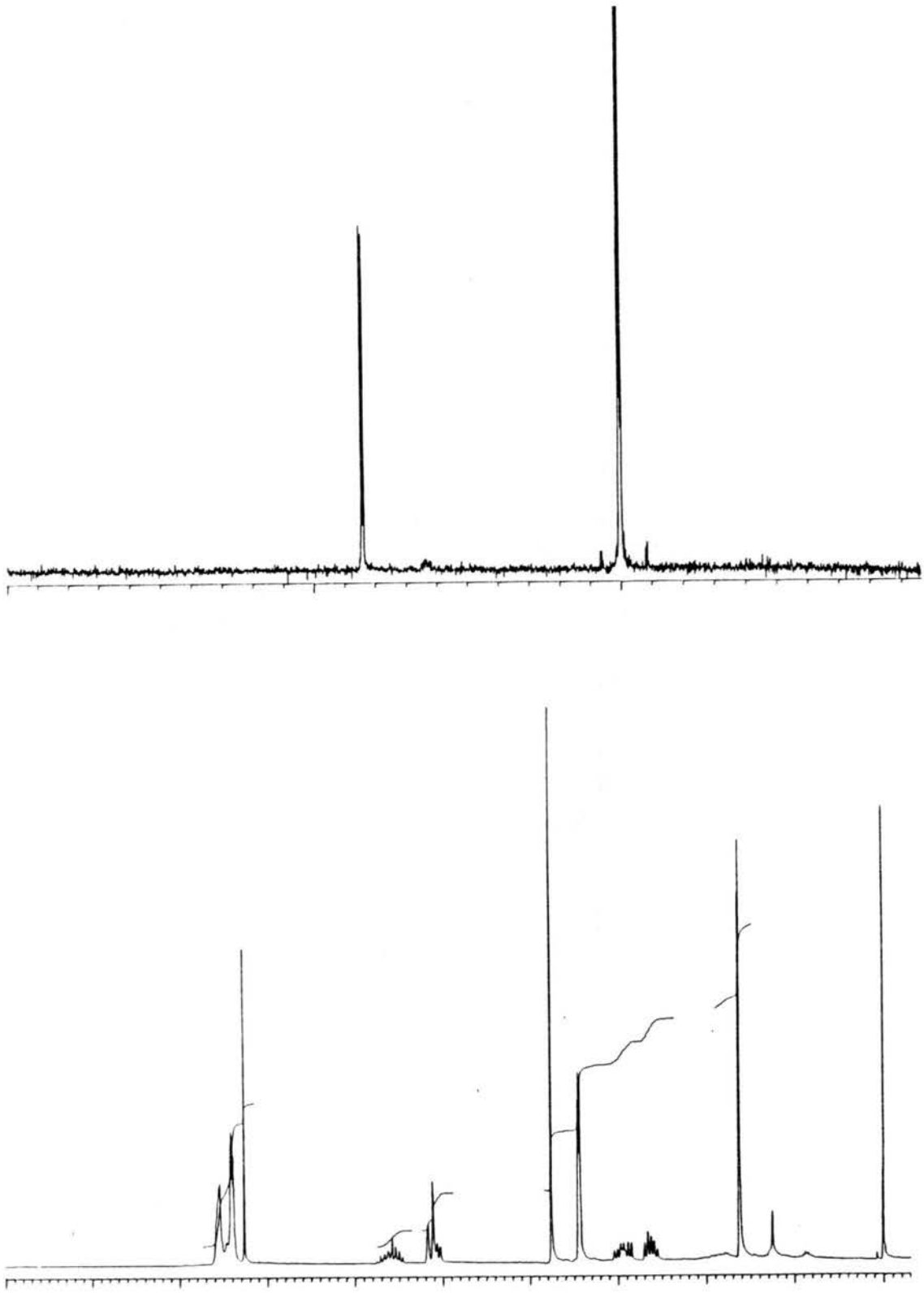


FIGURE 16a Racemic MPTA **215** ^{19}F and ^{1}H NMR

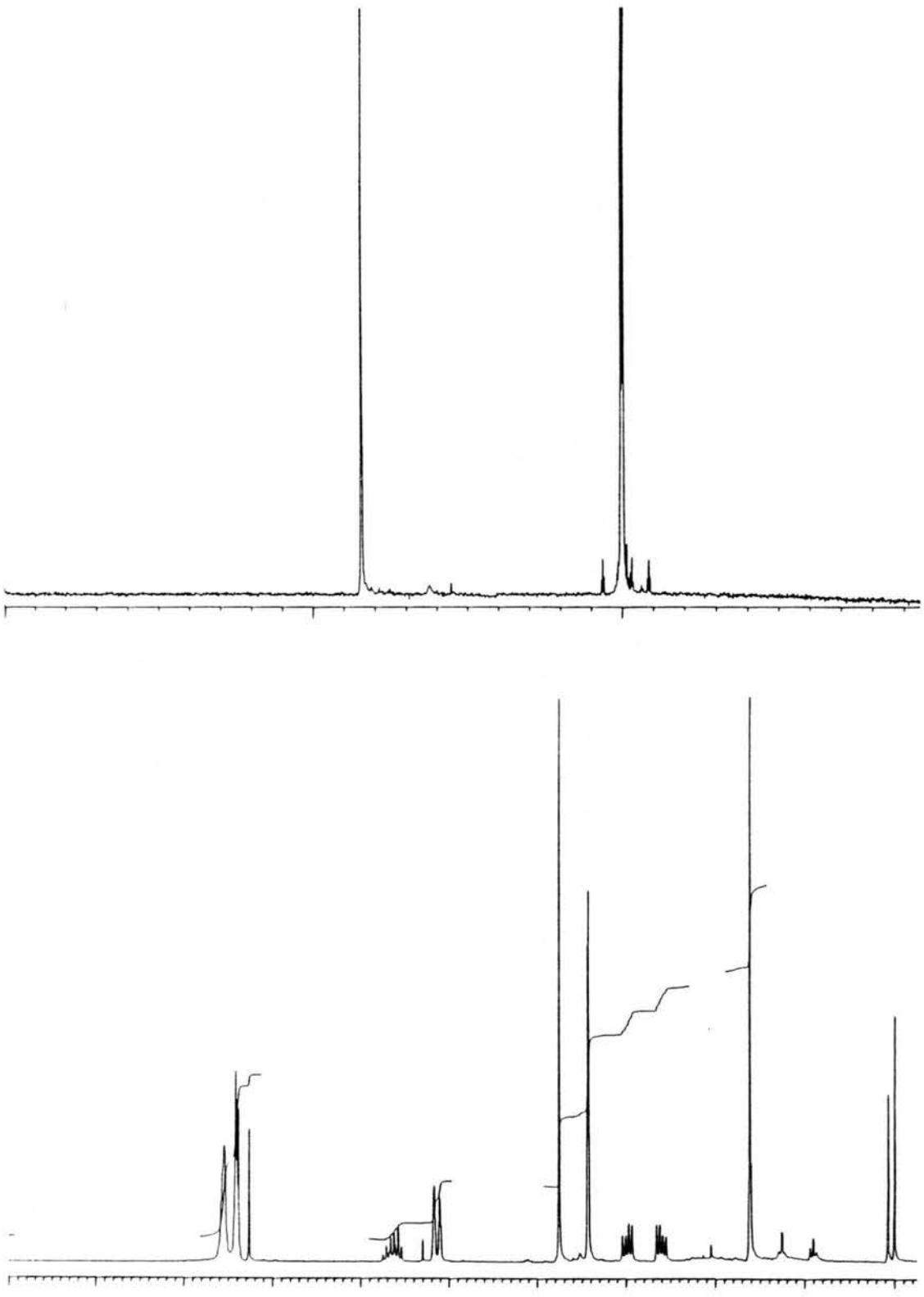


FIGURE 16b (+)-MPTA (Synthetic) **215** ^{19}F and ^{1}H NMR

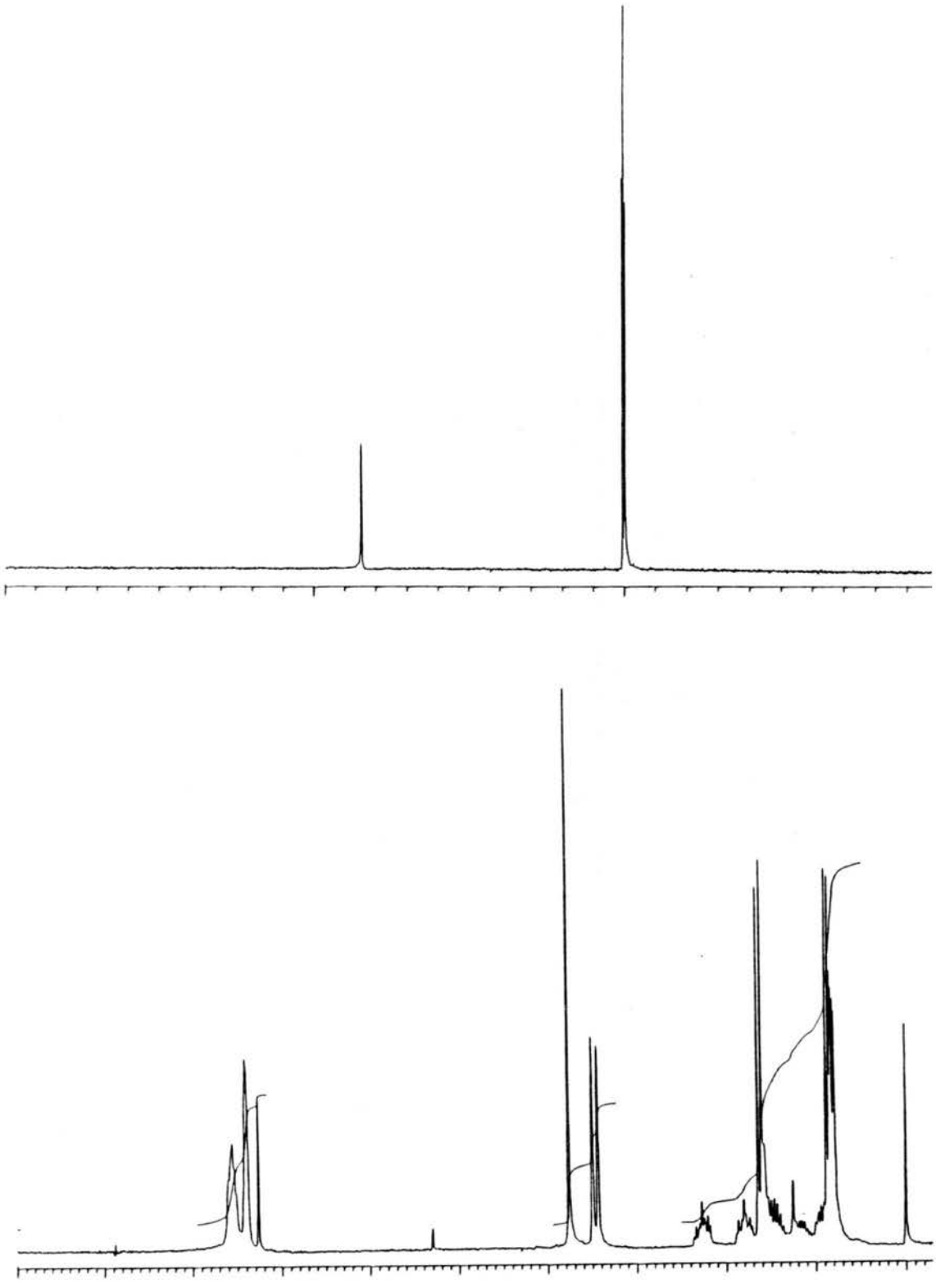


FIGURE 17a Racemic MPTA **216** ^{19}F and ^{1}H NMR

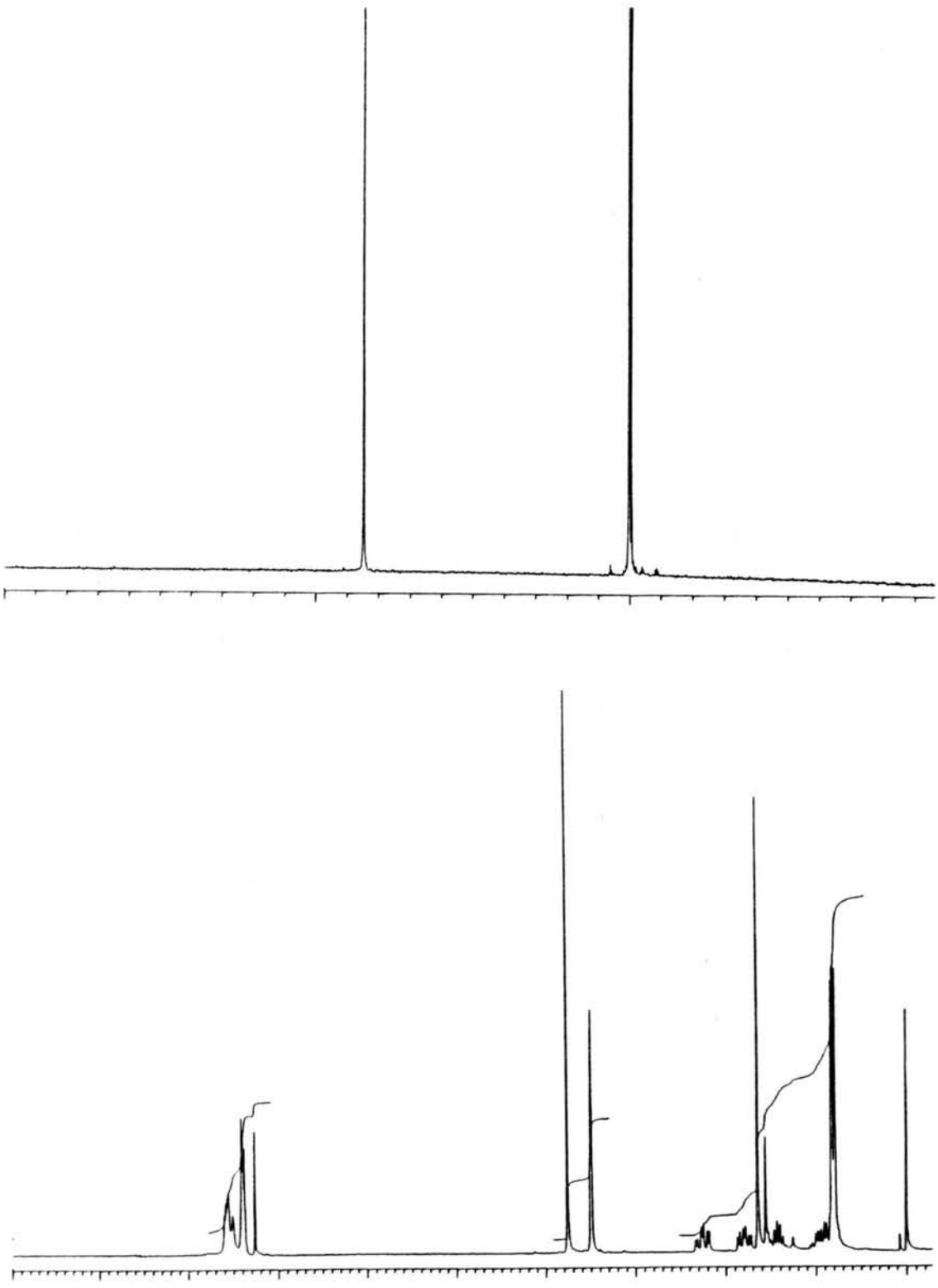


FIGURE 17b (-)-MPTA (Synthetic) **216** ^{19}F and ^{1}H NMR

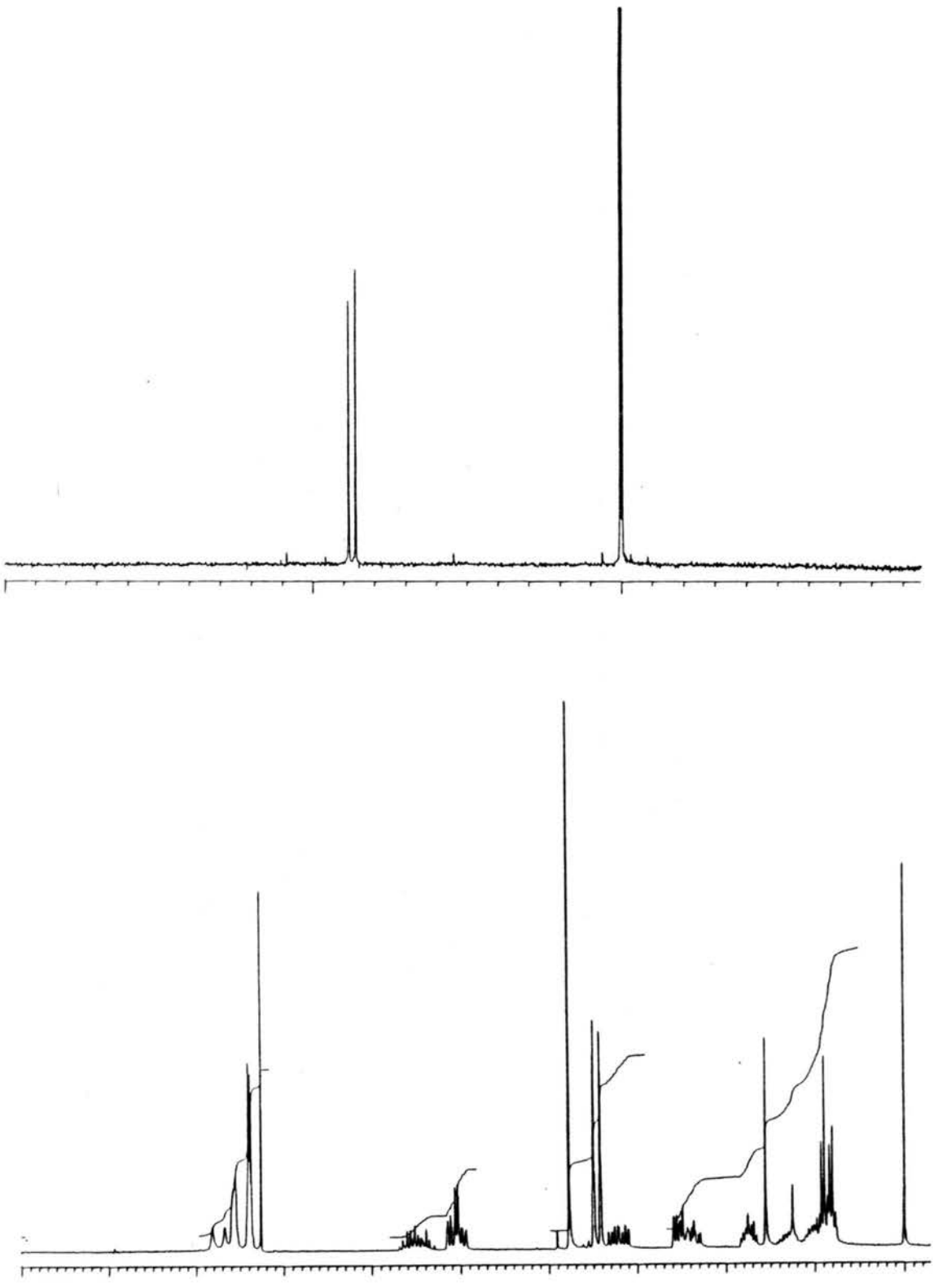


FIGURE 18a Racemic MPTA **218** ^{19}F and ^{1}H NMR

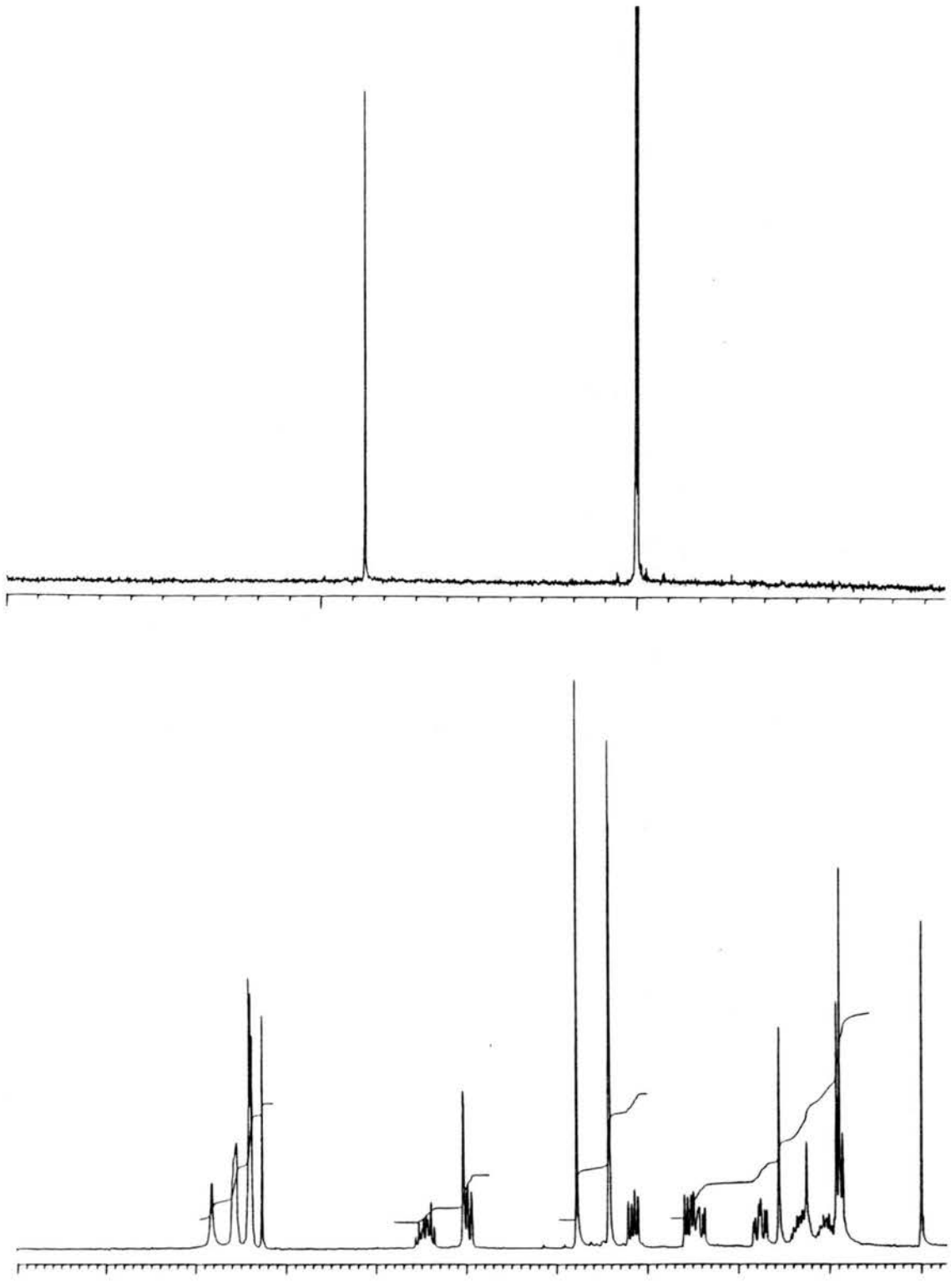


FIGURE 18b (-)-MPTA (Synthetic) **218** ^{19}F and ^{1}H NMR

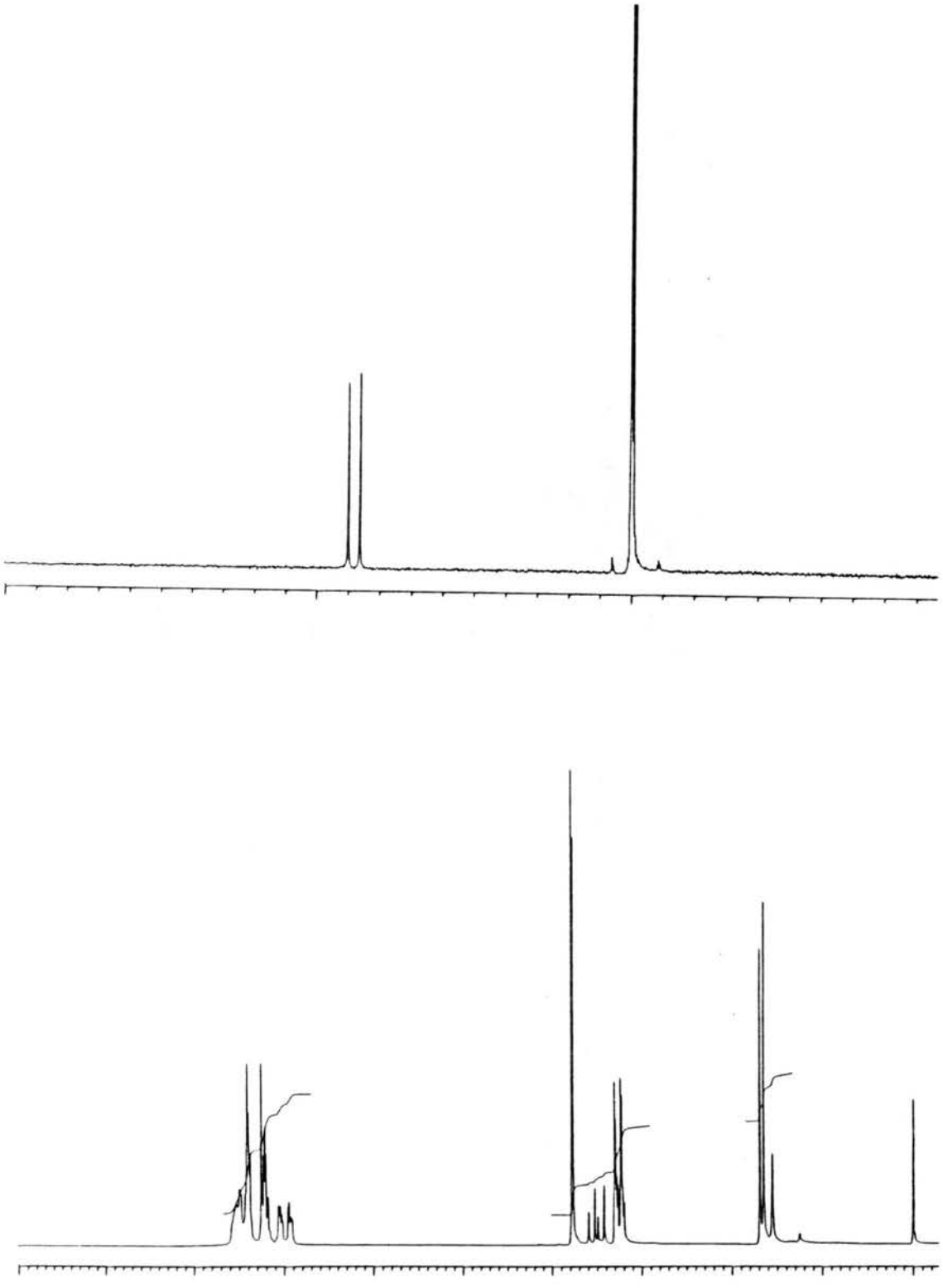


FIGURE 19a Racemic MPTA **220** ^{19}F and ^{1}H NMR

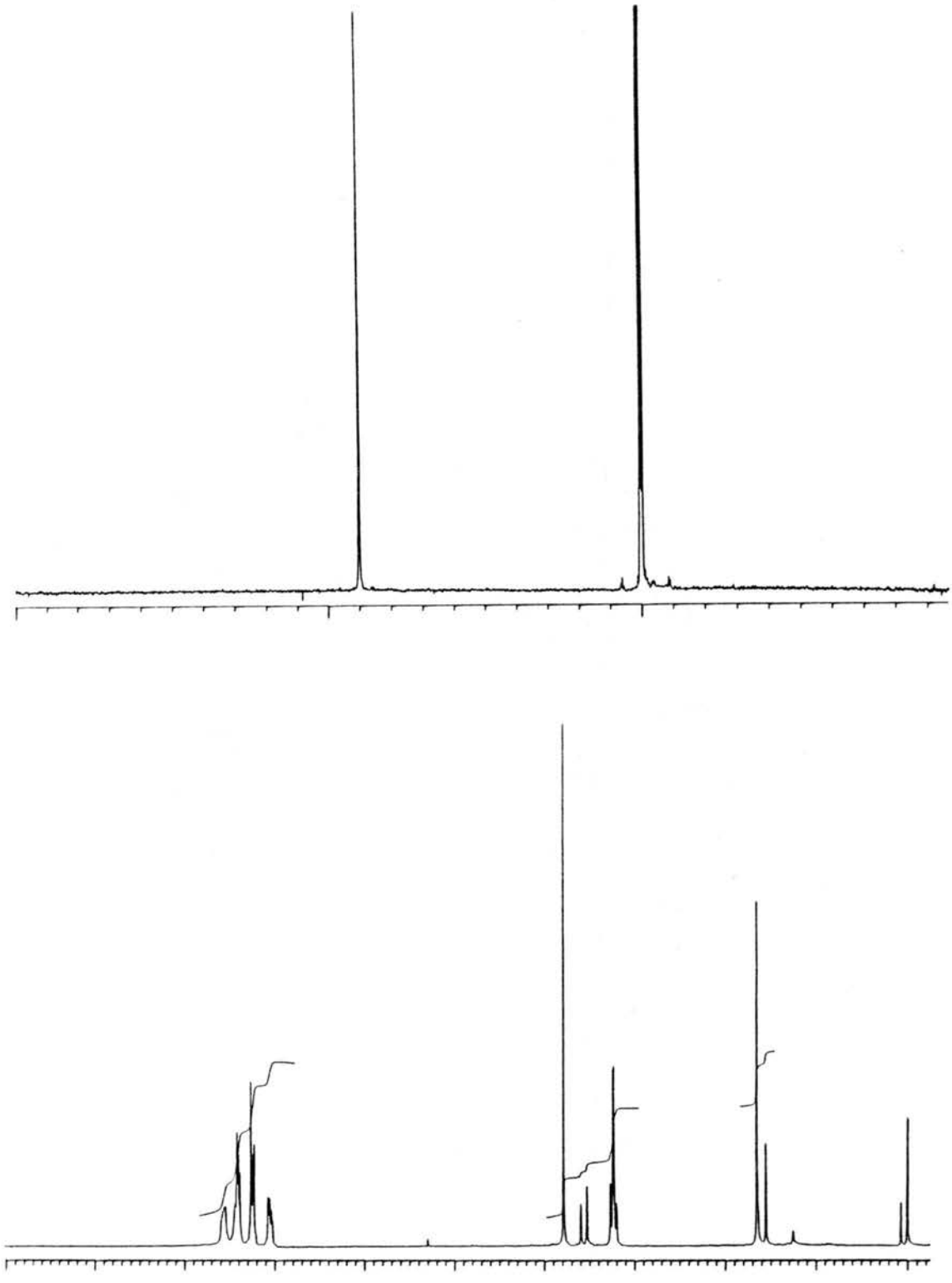


FIGURE 19b (+)-MPTA (Synthetic) **220** ^{19}F and ^{1}H NMR

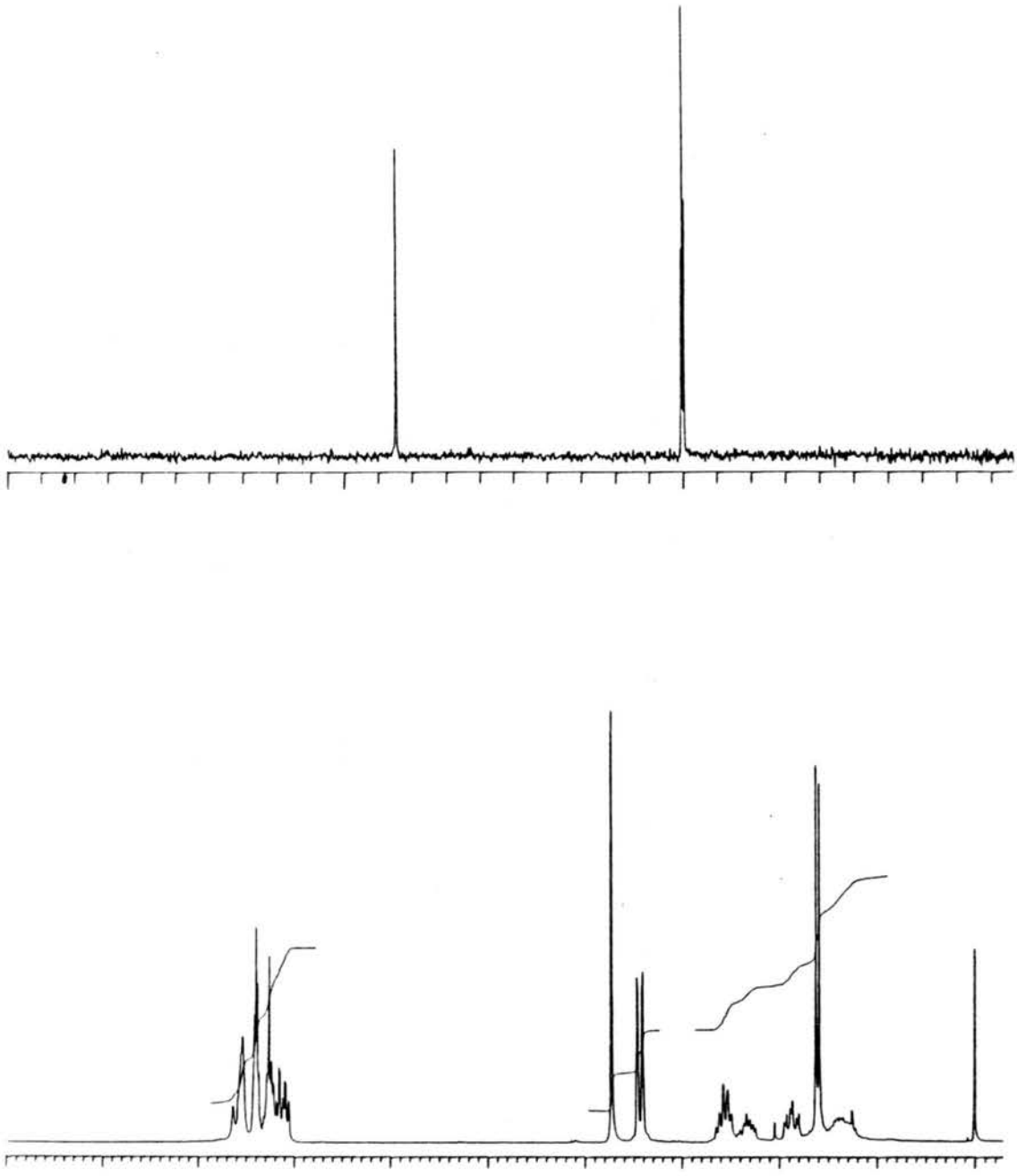


FIGURE 20a Racemic MPTA **222** ^{19}F and ^{1}H NMR

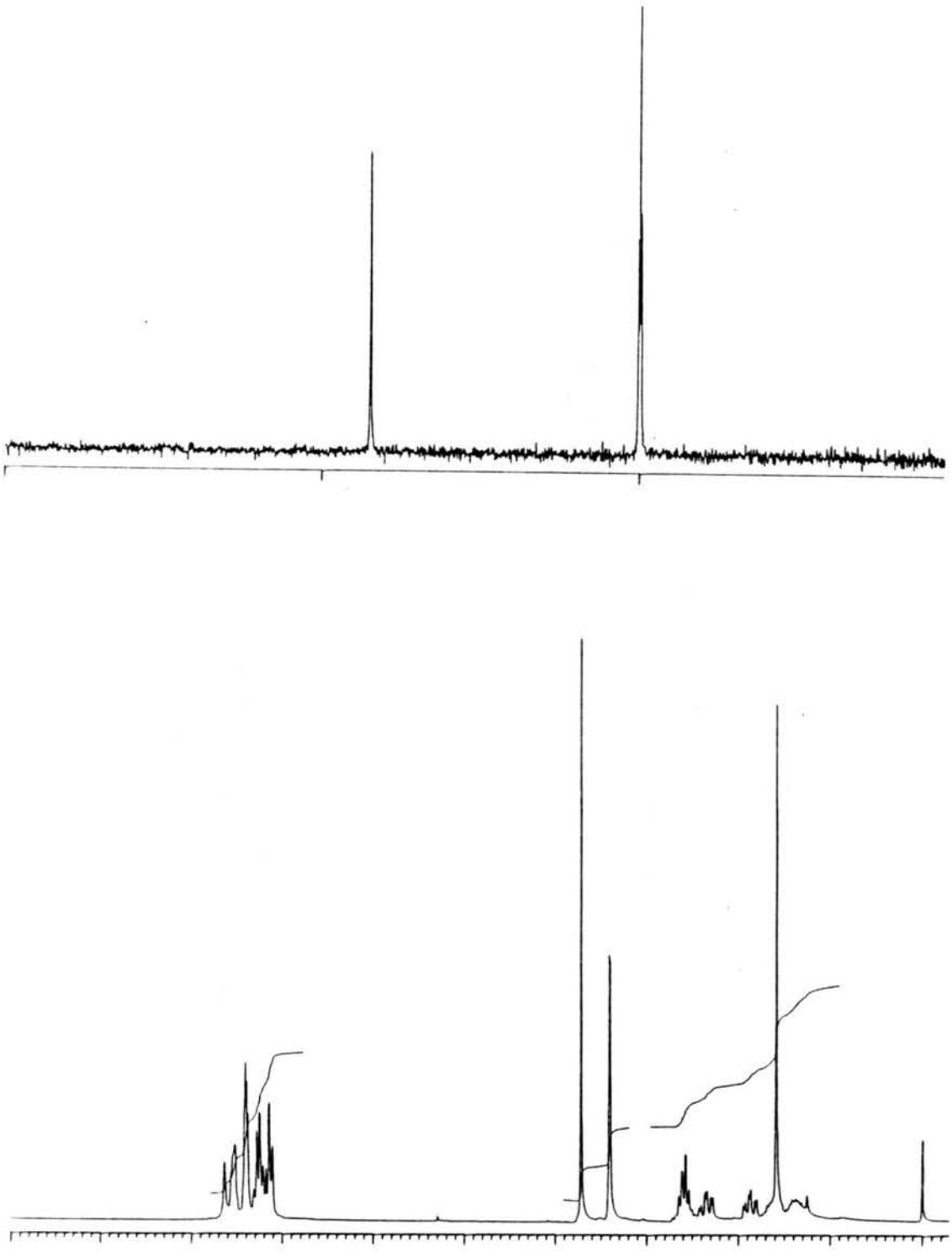


FIGURE 20b (+)-MPTA (Synthetic) **222** ^{19}F and ^{1}H NMR

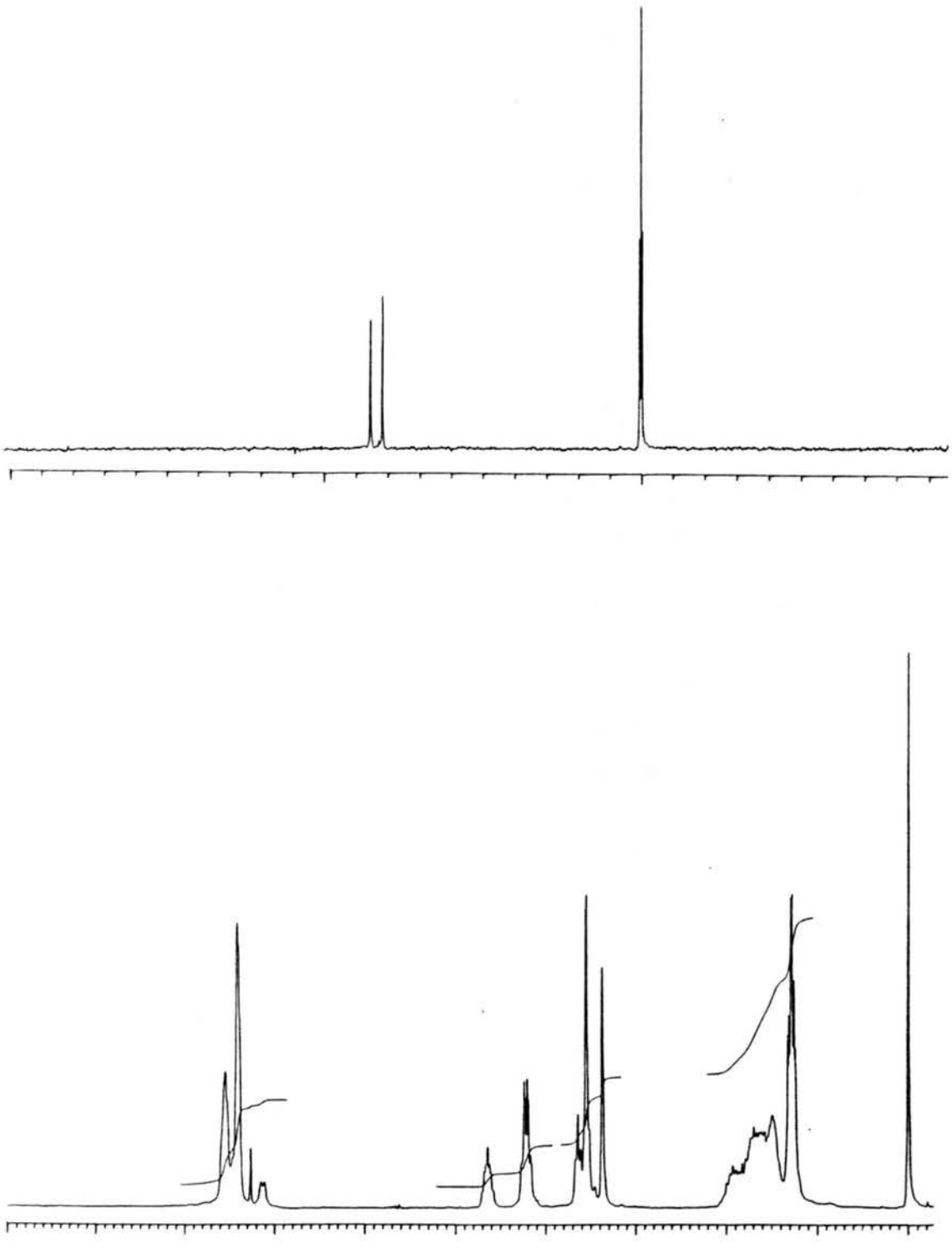


FIGURE 21a Racemic MPTA **236** ^{19}F and ^{1}H NMR

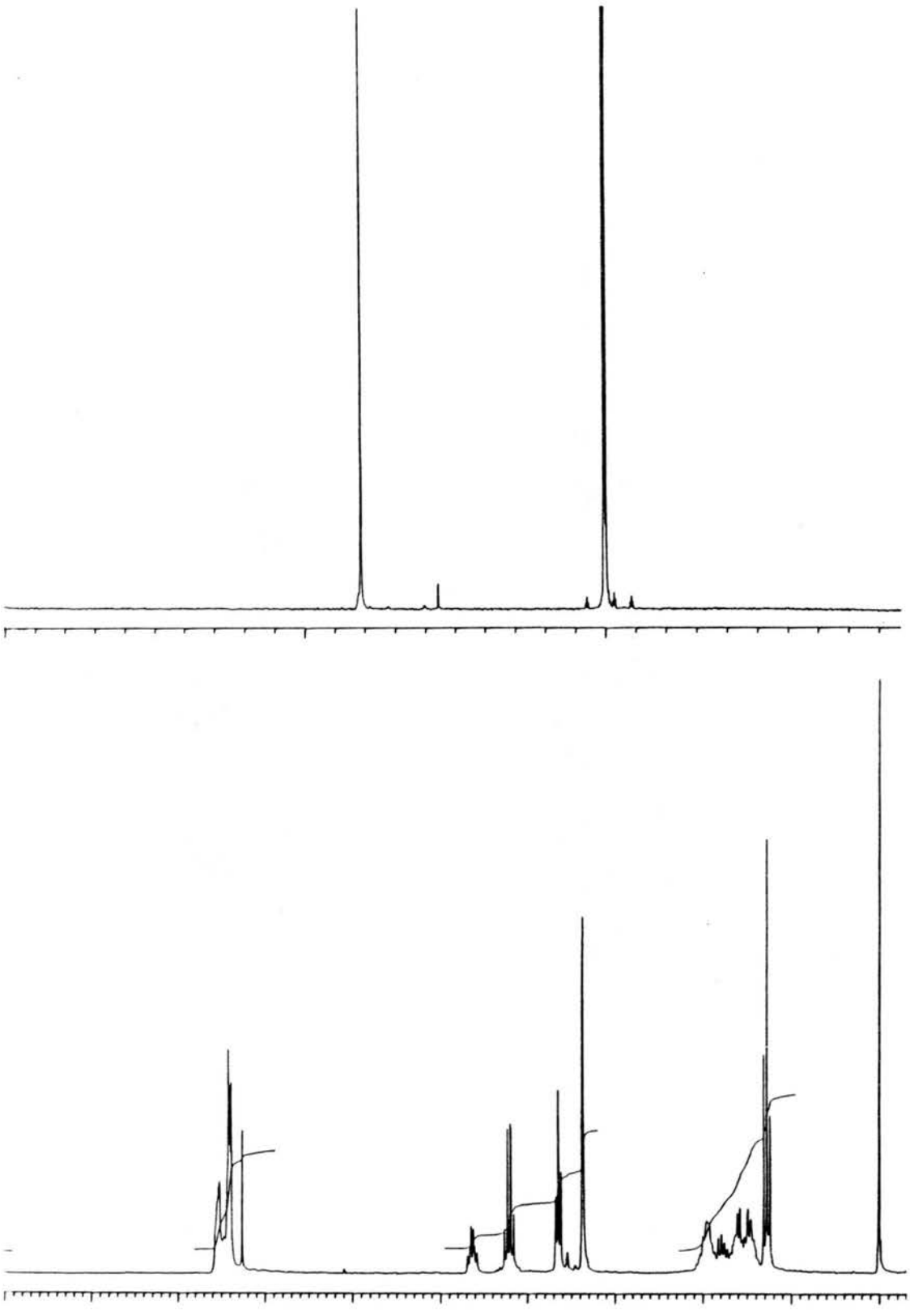


FIGURE 21b (+)-MPTA (Synthetic) **(D)-236** ^{19}F and ^{1}H NMR

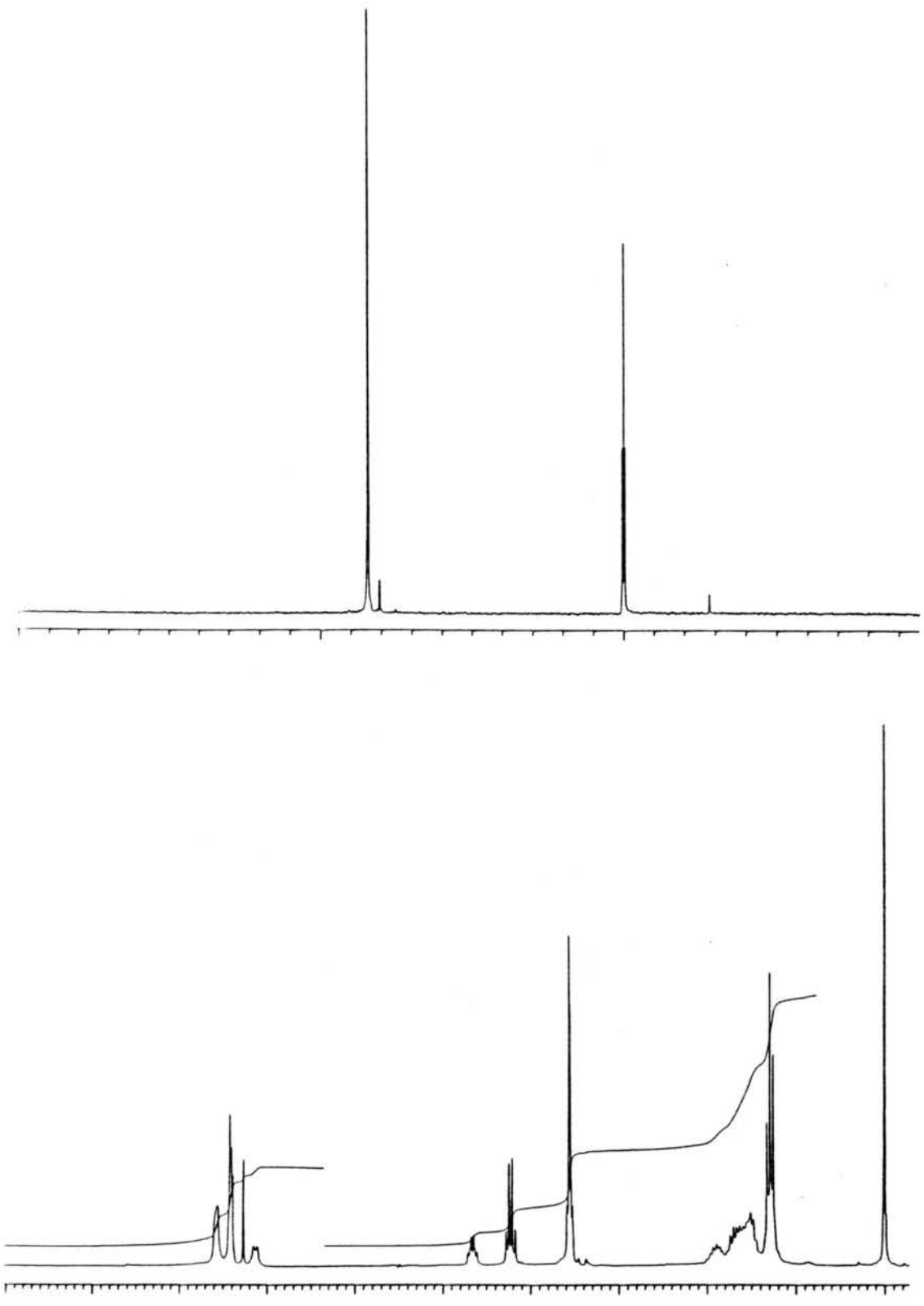


FIGURE 21c (+)-MPTA (Synthetic) **(L)-236** ^{19}F and ^{1}H NMR

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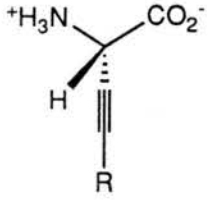
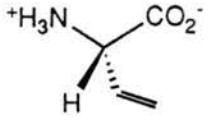
APPENDIX I

PERSPECTIVES ON THE REACTIVITY AND UTILITY OF GLYCINE ENOLATES DISCUSSED IN THIS DISSERTATION

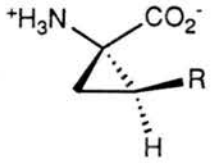
The lithium and sodium enolates generated from the oxazinones **166a/b** and **167a/b** smoothly undergo homologation with activated alkyl bromides and iodides such as $CH_2=CHCH_2Br$, $CH_2=CHCH_2I$, $Me_2C=CHCH_2Br$, CH_3I, $BrCH_2CO_2Et$ and $PhCH_2Br$ to afford the corresponding α-monoalkylated oxazinones. The enolates also couple with unactivated alkyl iodides. However, alkyl chlorides (even activated ones such as *m*-methoxybenzyl chloride, *p*-methoxybenzyl chloride, 3-chloro-2-methylpropene) are inert to the enolate alkylation. From these results, the following can be deduced. By employing this methodology of the enolate alkylations, it seems very difficult directly to prepare the biologically important amino acids such as alkynyl (**D**), vinyl (**E**), cyclopropyl (**F**) and aryl (**G**) glycines in optically active forms. The enolate alkylation with *sec*- and *tert*-alkyl halides (**H** and **I**) prone to hydrohalide elimination by base are also anticipated to be difficult.



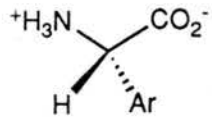
D



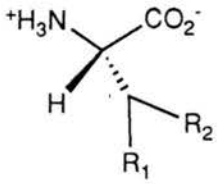
E



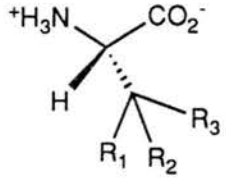
F



G



H



I

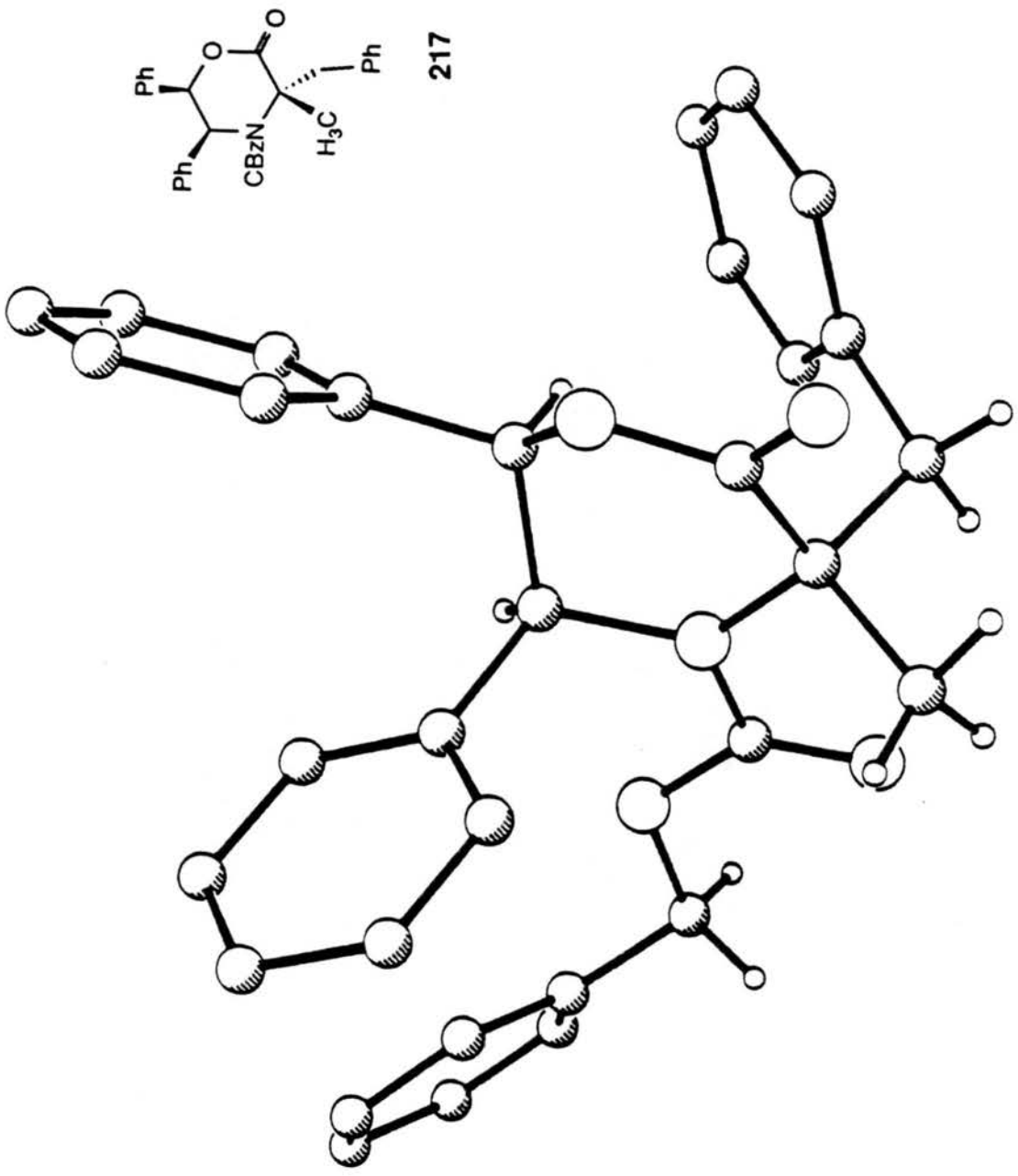
The boron enolates of the oxazinones **166a/b** and **167a/b** undergo coupling with aldehydes (even very hindered aldehydes such as **248** and

264) to provide the aldol products. The aldol condensation of the boron enolates with ketones have not been attempted yet.

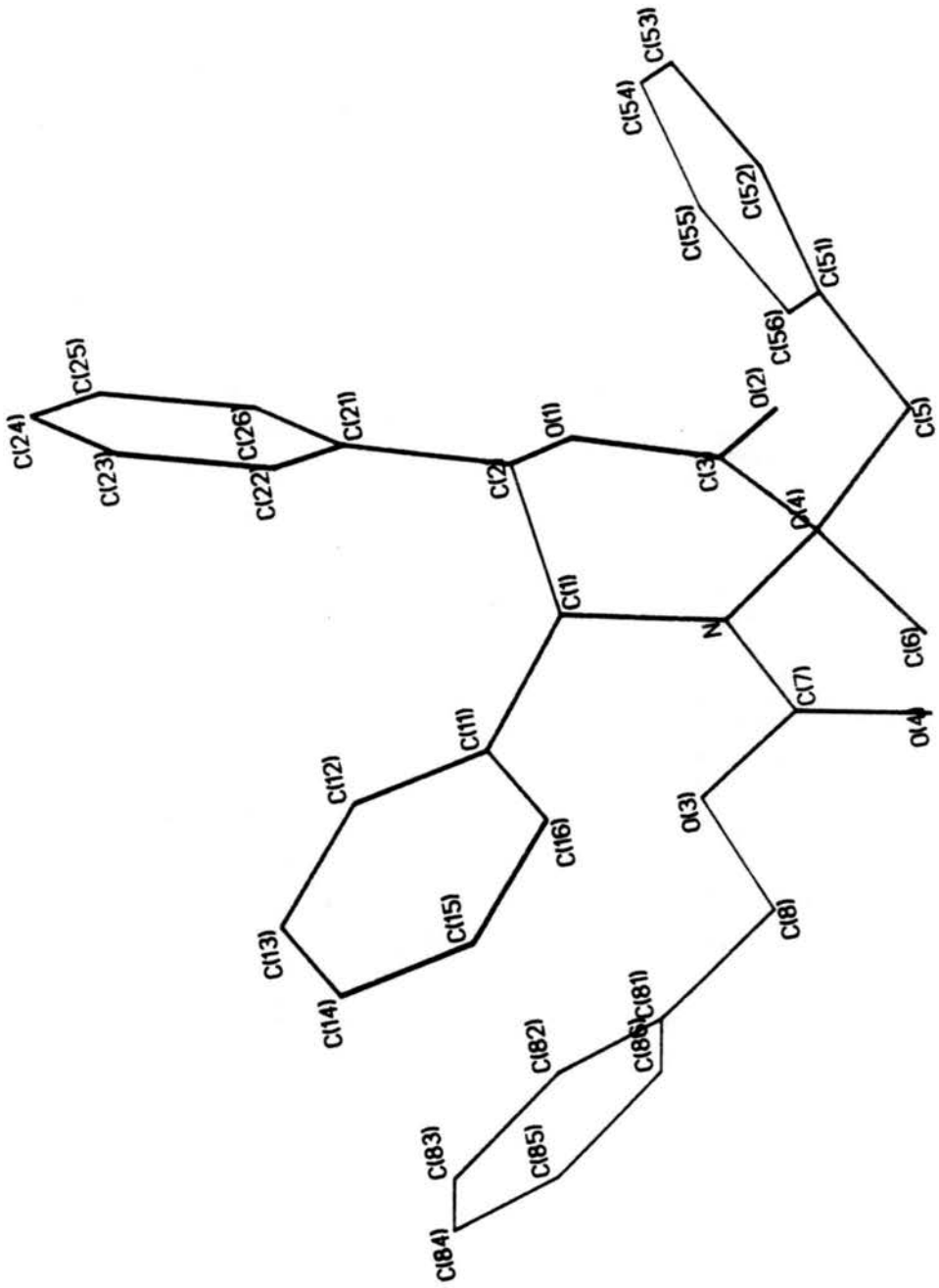
The potassium enolates generated from the α-monosubstituted oxazinones couple efficiently with activated alkyl bromides and iodides to furnish the corresponding α-disubstituted oxazinones. However, the second alkylation of the enolate with unactivated alkyl halides does not take place.

APPENDIX II

X-RAY ANALYSIS DATA FOR **217**



217


C(24)
C(25)
C(23)
C(26)
C(22)
C(21)
C(2)
O(1)
C(3)
O(2)
C(56)
C(55)
C(54)
C(53)
C(52)
C(51)
C(5)
O(4)
C(1)
N
C(6)
C(7)
O(4)
C(12)
C(11)
C(16)
C(13)
C(15)
C(14)
O(3)
C(8)
C(82)
C(81)
C(83)
C(85)
C(84)

Experimental. Crystals (colorless prisms) of $C_{32}H_{29}NO_4$ (hereafter **1**) obtained from M. Im and Professor Robert M. Williams (Colorado State University). Crystal size 0.12 × 0.19 × 0.24 mm. Nicolet *R*3*m* diffractometer, unit cell constants from least squares fit of setting angles for 25 reflections ($2\theta_{av}$ = 43.05°). Data collected (θ/2θ scans) to (sin θ)/λ = 0.5992 Å^{-1}, $0 \le h \le 8$, $0 \le k \le 17$, $0 \le l \le 26$. Three standard reflections (200, 040, 006) every 97, no change in intensity; Lorentz and polarization corrections; no absorption correction applied; 1918 unique reflections, 1361 reflections with $F_o > 2.5\sigma(F_o)$ observed.

Structure solved by direct methods (SOLV) in $P2_12_12_1$; block diagonal (max. 103 parameters/block, 289 parameters total, data/parameters = 4.7) weighted [$w = (\sigma^2(F) + gF^2)^{-1}$, $g = 2.3 \times 10^{-3}$] least-squares refinement on *F*. H atoms in idealized positions (C–H = 0.96 Å, $U(H) = 1.2 \times U_{iso}(C)$). All non-H atoms refined with anisotropic thermal parameters. Four phenyl rings modeled as rigid groups (C–C = 1.395 Å). At convergence ($(\Delta/\sigma)_{max}$ = 0.183, $(\Delta/\sigma)_{mean}$ = 0.044 for last 3 cycles) *R* = 0.085, *wR* = 0.091, *S* = 1.223, slope of normal probability plot = 1.028, $(\Delta\rho)_{max}$ = 0.30 e Å^{-3}, $(\Delta\rho)_{min}$ = –0.34 e Å^{-3}. Known stereochemistry at C(1) (*S*) and C(2) (*R*) (Im, 1990) from synthetic precursor gave relative stereochemistry at C(4) (*S*) and fixed the enantiomorph. Neutral atom scattering factors and anomalous dispersion corrections used (*International Tables for X-Ray Crystallography*, 1974); all calculations performed using SHELXTL program library (Sheldrick, 1983). Table 1 gives atomic coordinates, Tables 2 and 3 give bond lengths and angles,

Table 1. Atomic coordinates and isotropic thermal parameters ($Å^2 x 10^3$) for 1

	x	y	z	U
C(1)	0.7117(12)	0.9047(4)	0.1521(3)	31(3)*
C(2)	0.6616(12)	0.8418(5)	0.1977(3)	36(3)*
C(3)	0.3486(16)	0.8214(7)	0.1571(5)	64(4)*
C(4)	0.4340(13)	0.8281(6)	0.0986(4)	52(4)*
C(5)	0.4650(13)	0.7381(5)	0.0743(4)	48(3)*
C(6)	0.2775(15)	0.8733(7)	0.0627(4)	73(5)*
C(7)	0.6996(13)	0.9014(5)	0.0485(3)	41(3)*
C(8)	0.9168(15)	0.9899(5)	0.0025(3)	56(4)*
N	0.6149(10)	0.8787(4)	0.0990(3)	38(3)*
O(1)	0.4528(10)	0.8350(4)	0.2043(3)	50(2)*
O(2)	0.1854(10)	0.7988(5)	0.1627(3)	86(3)*
O(3)	0.8446(8)	0.9555(3)	0.0552(2)	38(2)*
O(4)	0.6453(9)	0.8766(4)	0.0020(2)	58(2)*
C(12)	0.8291(8)	1.0419(4)	0.1928(2)	49(4)*
C(13)	0.8064	1.1268	0.2082	65(5)*
C(14)	0.6326	1.1679	0.1984	76(5)*
C(15)	0.4815	1.1240	0.1732	91(6)*
C(16)	0.5042	1.0391	0.1578	67(5)*
C(11)	0.6780	0.9980	0.1676	35(3)*
C(22)	0.6126(8)	0.9043(4)	0.2958(2)	48(4)*
C(23)	0.6833	0.9257	0.3492	68(5)*
C(24)	0.8722	0.9064	0.3634	51(4)*
C(25)	0.9904	0.8658	0.3243	58(4)*
C(26)	0.9197	0.8444	0.2709	48(4)*
C(21)	0.7308	0.8636	0.2567	28(3)*
C(52)	0.5415(9)	0.6380(4)	0.1542(3)	65(4)*
C(53)	0.6722	0.5902	0.1855	77(6)*
C(54)	0.8644	0.5881	0.1696	70(5)*
C(55)	0.9259	0.6336	0.1223	52(4)*
C(56)	0.7952	0.6814	0.0910	42(3)*
C(51)	0.6029	0.6835	0.1069	41(3)*
C(82)	0.9895(10)	1.1211(4)	0.0569(3)	55(4)*
C(83)	1.1057	1.1910	0.0683	67(5)*
C(84)	1.2776	1.2017	0.0391	92(6)*
C(85)	1.3332	1.1424	-0.0016	126(7)*
C(86)	1.2169	1.0725	-0.0130	107(7)*
C(81)	1.0451	1.0618	0.0162	54(4)*

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 2. Bond lengths (A) for 1

C(1)-C(2)	1.505(11)	C(1)-N	1.482(10)
C(1)-C(11)	1.533(9)	C(2)-O(1)	1.471(11)
C(2)-C(21)	1.515(10)	C(3)-C(4)	1.511(14)
C(3)-O(1)	1.349(13)	C(3)-O(2)	1.202(14)
C(4)-C(5)	1.543(13)	C(4)-C(6)	1.556(14)
C(4)-N	1.494(12)	C(5)-C(51)	1.504(11)
C(7)-N	1.379(10)	C(7)-O(3)	1.333(10)
C(7)-O(4)	1.226(10)	C(8)-O(3)	1.447(10)
C(8)-C(81)	1.479(12)		

Table 3. Bond angles (deg) for 1

C(2)-C(1)-N	108.6(6)	C(2)-C(1)-C(11)	115.0(6)
N-C(1)-C(11)	113.4(6)	C(1)-C(2)-O(1)	110.8(7)
C(1)-C(2)-C(21)	115.9(6)	O(1)-C(2)-C(21)	103.6(6)
C(4)-C(3)-O(1)	122.2(9)	C(4)-C(3)-O(2)	119.7(10)
O(1)-C(3)-O(2)	118.0(10)	C(3)-C(4)-C(5)	109.4(8)
C(3)-C(4)-C(6)	104.7(8)	C(5)-C(4)-C(6)	108.5(8)
C(3)-C(4)-N	111.4(8)	C(5)-C(4)-N	111.9(7)
C(6)-C(4)-N	110.7(7)	C(4)-C(5)-C(51)	115.1(7)
N-C(7)-O(3)	112.9(7)	N-C(7)-O(4)	124.0(8)
O(3)-C(7)-O(4)	123.1(7)	O(3)-C(8)-C(81)	108.0(6)
C(1)-N-C(4)	122.6(6)	C(1)-N-C(7)	117.7(7)
C(4)-N-C(7)	119.7(6)	C(2)-O(1)-C(3)	117.3(7)
C(7)-O(3)-C(8)	113.7(6)	C(1)-C(11)-C(12)	117.4(4)
C(1)-C(11)-C(16)	122.6(4)	C(2)-C(21)-C(22)	121.7(4)
C(2)-C(21)-C(26)	118.3(4)	C(5)-C(51)-C(52)	120.4(4)
C(5)-C(51)-C(56)	119.5(4)	C(8)-C(81)-C(82)	119.6(4)
C(8)-C(81)-C(86)	120.4(4)		

Table S-1. Anisotropic thermal parameters ($Å^2 x 10^3$) for 1

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	28(5)	32(5)	31(5)	-0(4)	5(5)	8(5)
C(2)	32(6)	35(5)	42(5)	-12(4)	9(5)	8(5)
C(3)	52(8)	69(8)	71(8)	-33(7)	30(7)	0(7)
C(4)	29(6)	74(7)	53(6)	-24(6)	0(6)	-7(6)
C(5)	29(5)	57(6)	57(6)	-31(5)	15(5)	8(6)
C(6)	43(7)	90(8)	86(8)	-49(7)	-26(7)	28(7)
C(7)	34(6)	55(6)	34(5)	-19(5)	11(5)	23(5)
C(8)	78(9)	58(6)	30(5)	8(5)	15(6)	9(7)
N	36(5)	52(5)	26(4)	-16(4)	[illegible]	[illegible]
O(1)	44(4)	58(4)	48(4)	-17(4)	20(4)	-17(4)
O(2)	26(4)	119(7)	112(6)	-65(6)	34(5)	-25(5)
O(3)	39(4)	50(4)	26(3)	2(3)	2(3)	7(4)
O(4)	52(5)	89(5)	32(3)	-30(4)	-10(4)	14(4)
C(12)	70(8)	38(6)	39(5)	-7(5)	-4(6)	-5(7)
C(13)	94(10)	46(7)	56(6)	-5(6)	-5(8)	-11(8)
C(14)	139(13)	57(7)	30(6)	-5(5)	-9(8)	36(10)
C(15)	129(13)	87(9)	58(7)	-18(7)	-25(9)	78(10)
C(16)	71(9)	78(8)	54(6)	-26(6)	-23(7)	31(8)
C(11)	45(7)	35(5)	24(5)	-6(4)	4(5)	-1(6)
C(22)	71(8)	55(6)	19(5)	-3(4)	22(6)	6(7)
C(23)	108(10)	62(7)	33(6)	3(5)	25(8)	35(8)
C(24)	86(9)	35(6)	32(5)	-2(5)	-4(6)	5(7)
C(25)	88(9)	42(6)	44(6)	4(5)	-18(7)	-1(7)
C(26)	70(8)	39(6)	36(6)	5(5)	7(6)	0(6)
C(21)	45(6)	16(5)	25(5)	1(4)	3(5)	-11(5)
C(52)	80(9)	42(7)	73(7)	-27(6)	46(8)	-15(7)
C(53)	133(13)	51(7)	48(7)	0(6)	18(9)	-14(10)
C(54)	106(12)	30(6)	73(8)	-9(6)	-18(8)	-11(8)
C(55)	56(7)	57(7)	44(6)	-14(6)	-2(6)	-9(7)
C(56)	41(6)	43(6)	43(6)	-12(5)	9(5)	-0(6)
C(51)	41(6)	38(6)	43(6)	-15(5)	9(5)	-17(5)
C(82)	69(8)	49(6)	47(6)	8(6)	19(6)	24(7)
C(83)	93(10)	58(8)	50(7)	10(6)	25(7)	25(8)
C(84)	147(14)	45(8)	84(9)	-12(6)	8(10)	-41(9)
C(85)	158(15)	98(11)	123(12)	-18(10)	93(12)	-60(12)
C(86)	152(15)	63(8)	106(10)	-13(8)	88(11)	-36(10)
C(81)	88(9)	38(6)	35(5)	11(5)	25(6)	18(7)

The anisotropic temperature factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$.

Table S-2. H-Atom coordinates ($x10^4$) and isotropic thermal parameters ($Ax10^3$) for 1

	x	y	z	U
H(1)	8480	9028	1469	27
H(2)	7245	7915	1844	55
H(5A)	5127	7432	364	43
H(5B)	3431	7099	738	43
H(6A)	3181	8696	240	87
H(6B)	2405	9307	711	87
H(6C)	1704	8362	687	87
H(8A)	9866	9471	-178	62
H(8B)	8122	10097	-203	62
H(12)	9487	10136	1995	80
H(13)	9104	11570	2256	80
H(14)	6169	12263	2090	80
H(15)	3618	11523	1665	80
H(16)	4002	10089	1405	80
H(22)	4826	9175	2861	80
H(23)	6019	9536	3761	80
H(24)	9208	9211	4001	80
H(25)	11204	8525	3341	80
H(26)	10010	8164	2440	80
H(52)	4092	6394	1651	80
H(53)	6299	5589	2180	80
H(54)	9544	5552	1911	80
H(55)	10582	6322	1113	80
H(56)	8375	7127	585	80
H(82)	8712	11137	770	80
H(83)	10675	12318	963	80
H(84)	13576	12498	470	80
H(85)	14514	11498	-217	80
H(86)	12552	10317	-410	80

APPENDIX III

REPRINT

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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS: COMPARISON OF ENOLATE VS. CATION FUNCTIONALIZATION OF N-BOC-5,6-DIPHENYL-2,3,5,6-TETRAHYDRO-4H-1,4-OXAZIN-2-ONES

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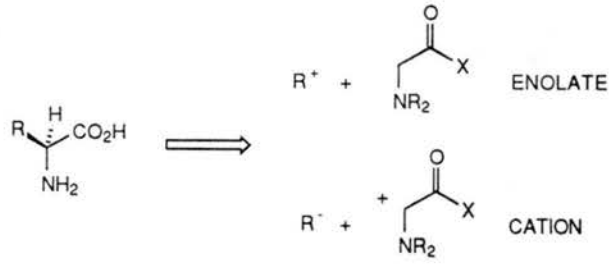
Abstract: Enolate generation and subsequent alkylation of the chiral glycinates **1** and **2** occurs with a high degree of diastereoselectivity. Reduction of the homologation products (**3** and **4**) furnishes with high enantiomeric excess, the N-t-BOC, and free α-amino acid derivatives **5** and **6**, respectively.

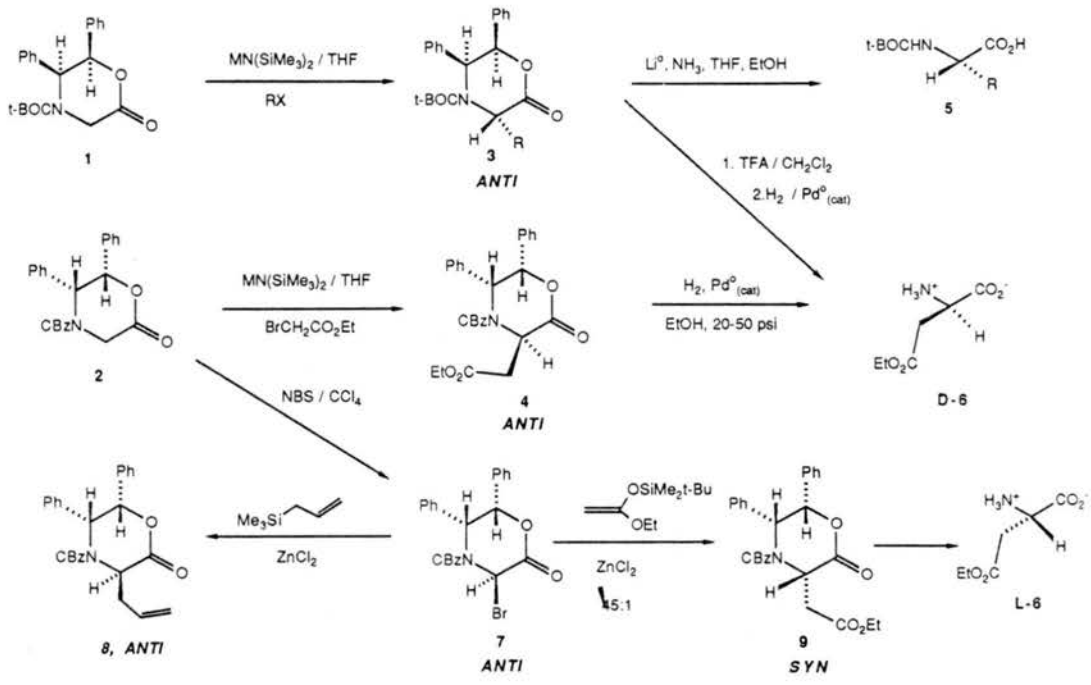
Numerous new and useful approaches to the asymmetric synthesis of α-amino acids have appeared in recent years.[1] Notable amongst these are several chiral, non-racemic glycine enolate equivalents[2] and glycine cation equivalents.[3] The attractiveness of these asymmetric glycine equivalents is the inherent versatility in preparing a diverse array of amino acids from a few common precursors with the appropriate C-C bond-forming technology. Schöllkopf and collaborators[4] have shown that their extensively studied enolate-based bis-lactam ether templates can also serve as glycine cation equivalents.

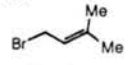
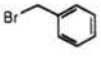
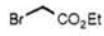


We have published[3] on the utility of the oxazinones **1** and **2** to function as versatile glycine cations *via* NBS bromination to the corresponding electrophilic α-bromo species. Numerous attempts at generating the enolate anions from **1** and **2** (LDA; THF; -100° ~-78°C; NaH; KOt-Bu; etc.) resulted in instantaneous decomposition and no detectable alkylation or deuteration products being isolable.[3] We have now found that the lithium or sodium salts of hexamethyldisilazane in THF at low temperature effects the clean deprotonation of these substrates without the significant decomposition that accompanied the other bases examined. The enolate anions derived from **1** and **2** can be stereoselectively alkylated with a high degree of diastereoselectivity (typically >99%) furnishing the crystalline *anti*-lactones **3** and **4** in good yield. As previously reported,[3] the N-t-BOC

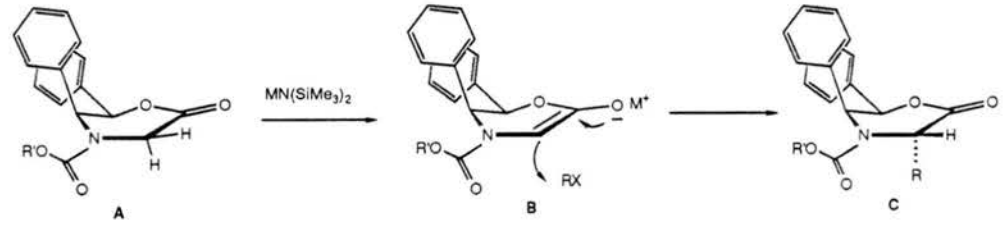
6076

SCHEME 1



ENTRY	LACTONE SUBSTRATE / YIELD 1	2	RX	AMINO ACID DERIVATIVE YIELD 5	6	%ee
1	91		MeI	54		97.2
2	48 (60)			50-70		98
3	68 (85)			52		100
4	70 (77)				76	98.2
5		61 (77)			71	95.9

SCHEME 2



substrates can be directly converted into the corresponding N-t-BOC amino acids (**5**) by dissolving metal reduction (Table, entries 1-3). In the case of dissolving metal-reducible functionality, hydrogenation over a Pd° catalyst directly provides the zwitterions (**6**, Table entries 4 and 5). In all cases, the % ee exceeded 95%.

It is worthwhile to compare the complementary cationic and anionic reactivities of the templates (**1**/**2**) for constructing variously substituted α-amino acids. The amino acids alanine and allyl glycine have been prepared from the electrophilic route by use of CH_3ZnCl and allyltrimethylsilane couplings, respectively. In both cases, the *anti*-oxazinones (**3**) are produced. The same relative stereochemical result is realized with CH_3I and allyl bromide (entries 1, 2) alkylation of the enolate derived from **1**. However, the yield of the CH_3I alkylation (91%) is far superior to the CH_3ZnCl coupling to the α-bromolactone (46%) due to a competing 1-electron reduction pathway observed for the more basic organometallic reagents. The allyl case is more or less equal for either approach. In the case of the bromoethyl acetate alkylation (entry 5) the *anti*-oxazinone (**4**) is obtained as the exclusive product. Amino acid[5] L-**6** was also obtained (in similar yield and % ee) by coupling the ketene silyl acetal of ethyl acetate to the electrophilic system (**7**) and reduction. However, a 45:1 ratio of *syn*:*anti* products results *via* an S_N2' displacement of the *anti*-α-bromide (**7**) derived from **2** in this coupling. Thus, *either* optical isomer of **6** can be obtained in high enantiomeric excess from the *same* optical antipode of **2** by simply choosing either electrophilic or nucleophilic chemistry. The enolate approach discussed herein, also gives access to the phenylalanine manifold (entry 4) which was not readily achieved from the electrophilic system.

The stereoselectivity of these enolate alkylations can be readily rationalized by considering the conformer **B** that disposes the phenyl ring in a 1,3-relation to the enolate carbon in a pseudoaxial orientation; the electrophile simply approaches from the less hindered face giving the observed *anti*-oxazinones. What is less strightforward, is the observed failure of bases such as LDA and the consistent success of either Li- or $NaN(SiMe_3)_2$ to effect *stable* enolate generation and subsequent alkylation. Several examples[6] of the success of hexamethyldisilazane bases over LDA have been reported, but in the context of cation effects. The underlying reasons for the anomaly in the present case are being investigated.

The present technology nicely complements the electrophilic couplings[3] and should substantially expand the intrinsic versatility of these commercially available templates for amino acid synthesis.

A typical procedure for enolate alkylation is as follows: To a stirred solution of **1** (500 mg, 1.4 mmol, 1.0 eq) in THF (10 mL) at -100°C was added $NaN(SiMe_3)_2$ (1.4 mmol, 1 eq as a 1M THF solution) dropwise. The mixture was stirred for 30 min. at -100°C and 1-bromo-3-methyl-2-butene (500 μL, 4.3 mmol, 3 eq) was added. The solution was stirred an additional 40 min. at -100°C, poured into H_2O and thoroughly extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial PTLC silica gel chromatography (CH_2Cl_2 eluent) to afford 405 mg (68% or 85% based on consumed **1**) of **3** (R = dimethallyl) mp 150-151°C (recryst. Et_2O/hexanes) and 98 mg (19.6%) of unreacted **1**.

6078

^{1}H NMR (200 MHz) (DMSO - d_6, 398°K) δ TMS: 1.18 (9H, s); 1.68 (3H, s); 1.74 (3H, s); 2.73-3.01 (2H, m); 4.82 (1H, dd, J = 5.59 Hz, 5.64 Hz); 5.12 (1H, d, J = 2.75 Hz); 5.30 (1H, t, J = 7.62 Hz); 6.16 (1H, d, J = 3.11 Hz); 6.56 (2H, m); 7.01-7.28 (8H, m). $[\alpha]_D^{25}$ = -19.5° (C = 5.7, CH_2Cl_2). Anal. calcd for $C_{26}H_{31}NO_4$: C, 74.11; H, 7.36; N, 3.33. Found: C, 74.24; H, 7.32; N. 3.28. IR (KBr pellet): 1734, 1692 cm^{-1}.

General experimental conditions for dissolving metal reduction to the corresponding N-t-BOC derivative **5** are provided in ref. 3.

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References and Footnotes

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