DISSERTATION

ASYMMETRIC SYNTHESES OF CYCLOPROPANE-CONTAINING AMINO ACIDS

Submitted by

Glenn Jeffery Fegley

Department of Chemistry

In partial fulfillment of the requirements

for the degree of Doctor of Philosophy

Colorado State University

Fall 1994

COLORADO STATE UNIVERSITY

November 19, 1993

WE HEREBY RECOMMENND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY GLENN J. FEGLEY ENTITLED "ASYMMETRIC SYNTHESES OF CYCLOPROPANE-CONTAINING AMINO ACIDS" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Adviser

Department Head

ABSTRACT OF DISSERTATION

ASYMMETRIC SYNTHESES OF CYCLOPROPANE-CONTAINING AMINO ACIDS

Chiral, non-racemic (D)-erythro-4-(*tert*-butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one was efficiently condensed with various alkyl and aryl aldehydes via the Emmons-Horner-Wadsworth procedure to provide the corresponding (E)-α,β-dehydrolactones. These compounds were smoothly cyclopropanated by racemic sodium [(diethylamino)phenyl]oxosulfonium methylide to furnish in high chemical and optical yields the desired cyclopropyllactones. Interestingly, the ylide consistently delivered the methylene unit almost exclusively *syn* to the C-5 and C-6 phenyl rings of the α,β-dehydrolactones. Removal of the chiral auxiliary was accomplished by dissolving-metal reduction using lithium metal and liquid ammonia to afford the corresponding *t*-BOC-protected 2-alkyl-1-aminocyclopropane-1-carboxylic acids in good yield. Sequential treatment of these protected amino acids with anhydrous methanolic HCl (or aqueous HCl) and propylene oxide provided the corresponding free amino acids in high chemical and optical yields. In this fashion the asymmetric syntheses of (1S)-[2,2-$^2H_2$]ACC, (1S,2S)-MeACC (norcoronamic acid), (1S,2S)-EtACC (coronamic acid), (1S,2S)-PrACC, and three diastereomers of cyclopropyldiaminopimelic acid (cyclopropylDAP) were achieved in 83-99% de. Deblocking of a phenyl-substituted cyclopropyllactone was accomplished via a stepwise sequence involving the lead tetraacetate cleavage of the chiral auxiliary as the key step. This protocol furnished (1S,2R)-2-phenyl-1-aminocyclopropane-1-carboxylic acid in greater than 95% de, and revealed a potential route to other aromatic-substituted cyclopropane amino acids.

Finally, several (E)-α,β-dehydrolactones were treated with the azomethine ylide of N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine to furnish the corresponding spiropyrrolidine lactones in moderate to excellent yields and in high diastereomeric excesses. Deprotection of one spiropyrrolidine adduct by palladium-catalyzed hydrogenolysis resulted in the synthesis of enantiomerically pure (S)-(-)-cucurbitine.

Glenn J. Fegley
Department of Chemistry
Colorado State University
Fort Collins, CO 80523
November 19, 1993

ACKNOWLEDGEMENTS

During the course of my graduate studies at Colorado State University there have been several people who have contributed significantly to this work and who deserve my heartfelt appreciation. First, I must thank Dr. Peter Sinclair. His ground breaking studies in the asymmetric synthesis of amino acids provided a solid foundation for the success of the current work. Also, many thanks go to Drs. David Aldous, Paul Erhlich, Tomas Glinka, and Nobuyoshi Yasuda. These individuals provided a constant source of intellectual stimulation and were excellent role models, as exemplified by their hard work ethic. It is a privilege for me to have been associated with these fine people.

Past and present Williams' group members who deserve my sincerest gratitude for a number of reasons, include: Suzanne Aldous, Dr. Yusuke Amino, Dan Bond, Dr. Edi Brunner, Jinua Cao, Daimo Chen, Hazel Coffman, Catherine Durham, René Gallegos, Vic Jewell, Myeong-Neo Im, Drs. Mark and Lynn Kirms, Dr. Heedo Kim, Drs. Andrei and Eva Kwast, Jinhwa Lee, Dr. Mark Sabol, Steve Rubenstein, Sam Rollins, Dr. Gysoon Park, Prof. Juan Sanz-Cervera, Tracy Tippie, Jennifer Travers, Weixu Zhai, Dr. Matt Peterson, and Chenguang Yuan.

I wish to extend my gratitude to Gina Fabrizius for the many inconvenient errands she performed regarding the final preparation of this thesis and also for processing the necessary paperwork with the graduate school while I was in Indiana. Her assistance made my job a whole lot easier. I also wish to thank Dr. Chris Rithner, Don Dick, and Suzie Miller for their assistance in collecting ^{1}H NMR, Mass Spectroscopy, and X-ray crystal data, respectively.

Group members who formed the "laughs committee" and helped me keep my sanity during the difficult times of my graduate education are: Scott Rajski, Mark Flanagan, and Drs. Mary and Wendel Doubleday (Wendel was an honorary member of the Williams' group). This group of people could, through humor, lighten an otherwise darkened mood when I was having bad days in lab. I thank them for helping keep my morale up; they will be sorely missed.

I must also thank my colleagues who endured my many "Fegleyisms" (a term first coined by the late Professor John K. Stille and as yet ill-defined) over the years: Drs. Tim Cushing, Sean Esslinger, Jim Hendrix, and Greg Miknis. We shared many of the ups and downs in lab together and my affiliation with these four people has made me a better scientist and human being.

A special thank you goes to two cherished and reliable friends from outside the Williams' group, Dr. Daniel Romo of the Meyers' group and David Morita of the Norton group. I enjoyed and will miss the time I shared with Daniel and his family on Friday nights and occasional weekends. I must also thank Daniel for the occasional late night rides from Stapleton Airport to Fort Collins when I missed the last airport shuttle. I will miss the intense basketball and volleyball rivalry I had with Dave. Maybe ten years from now he will catch up to me in both sports! Of course I'm only joking.

Finally, I wish to extend my sincerest appreciation to Professor Robert M. Williams who unselfishly provided the financial and intellectual support during all of my graduate education. I have learned an incredible amount of science from him and thank him for the opportunity of working in his laboratories. He gave me the freedom to explore and develop an interesting area of asymmetric amino acid synthesis essentially without any constraints. In fact, much of the work described in this thesis was a direct result of my "tinkering" at the bench and was supported immensely by the creative input from Dr. Williams. I will miss the group social activities (e.g. summer picnics and the annual ski trip) sponsored by Dr. Williams. I am very fortunate to have been a member of the Williams' research group.

DEDICATION

I wish to dedicate this thesis to the people who count most in my life: Mom, Dad, Wayne, and Sherry. I sincerely appreciate their many long distance phone calls and letters during my stay in Fort Collins. Without their love and constant support none of this work would have been possible.

PREFACE

The author would like to inform the reader that a substantial portion of the research described in Chapter Two has been published in scientific journals prior to the preparation of this document. In this version some details have been added to better illustrate certain aspects of the research not previously described in the journal format.

Table of Contents

Chapter One (Introduction)

	page
1.1 Intoduction	2
1.2 Biology of Naturally Occurring 1-Aminocyclopropane-1-carboxylic Acids	3
1.3 Asymmetric Syntheses of 1-Aminocyclopropane-1-carboxylic Acids	9
1.4 Stereocontrolled Syntheses of 1-Aminocyclopropane-1-carboxylic Acids	26

Chapter Two (Results and Discussion)

2.1 Asymmetric Syntheses of (1S,2S)-2-Alkyl-1-aminocyclopropane-1-carboxylic Acids	31
2.2 Asymmetric Synthesis of (1S,2R)-2-Phenyl-1-aminocyclopropane-1-carboxylic Acid	48
2.3 Asymmetric Syntheses of (2S,3S,6S)-, (2S,3S,6R)-, and (2R,3R,6S)-2,3-Methano-2,6-diaminopimelic Acids	54
2.4 Asymmetric Synthesis of (S)-(-)-Cucurbitine	67
References	75
Chapter Three (Experimental)	86
3.1 Experimental Procedures and Data	87
3.2 NMR Spectra	129
3.3 X-ray Analysis Data	192

Abbreviations

ACC	1-aminocyclopropane-1-carboxylic acid
Ac_2O	acetic anhydride
AcOH	acetic acid
AIMSA	aminoiminomethanesulfonic acid
Ala	alanine
AZIDAP	2-(4-amino-4-carboxybutyl)-2-aziridinecarboxylic acid
BnOCOCl	benzyl chloroformate
t-BOC	*tert*-butoxycarbonyl
$(BOC)_2O$	di-*tert*-butyl dicarbonate
$BrCH_2CO_2Et$	ethyl bromoacetate
n-BuLi	*n*-butyllithium
t-BuOH	*tert*-butanol
t-BuOK	potassium *tert*-butoxide
Cbz	carbobenzyloxy
CbzCl	benzyl chloroformate (carbobenzyloxy chloride)
$CDCl_3$	deuterochloroform
(S,S)-CHIRAPHOS	(bicyclo[2.2.1]hepta-2,5-diene)[(2S,3S)-bis(diphenylphosphino)butane]rhodium perchlorate
Cys	cysteine
DAP	2,6-diaminopimelic acid
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAH	diisobutylaluminum hydride
(R,R)-DIPAMP	(cycloocta-1,5-diene)[(R,R)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOPA	3-(3,4-dihydroxyphenyl)-L-alanine
ee	enantiomeric excess
EFE	ethylene forming enzyme

EtCHO	propionaldehyde
Et_3N	triethyl amine
Et_2O	diethyl ether
EtOAc	ethyl acetate
$Et_3O^+BF_4^-$	triethyloxonium tetrafluoroborate
EtOH	ethanol
^{19}F NMR	fluorine nuclear magnetic resonance
Glu	glutamic acid
Gly	glycine
HMPA	hexamethylphosphoramide
^1H NMR	proton nuclear magnetic resonance
HRMS(FAB)	high resolution mass spectrum (fast atom bombardment)
HSCoA	coenzyme A (free sulfhydryl)
hυ	ultraviolet radiation
LDA	lithium diisopropylamide
Li°	lithium metal
$LiAlD_4$	lithium aluminum deuteride
$LiN(SiMe_3)_2$	lithium bis(trimethylsilyl)amide
MeCHO	acetaldehyde
MeCN	acetonitrile
Me_2CuLi	dimethyl cuprate
MEM	(2-methoxyethoxy)methyl
$Me_3O^+BF_4^-$	trimethyloxonium tetrafluoroborate
MeOH	methanol
$(MeO)_3P$	trimethylphosphite
p-MeOPhCHO	*para*-anisaldehyde
$3,5\text{-}(MeO)_2PhCHO$	veratraldehyde
Me_2S	dimethyl sulfide
Me_3SiI	iodotrimethylsilane
$Me_2SO(Me)I$	trimethylsulfoxonium iodide
α-methylDOPA	3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine
MHz	megahertz
MNNG	1-methyl-3-nitro-1-nitrosoguanidine
MsCl	methanesulfonyl chloride (mesyl chloride)

MTPA	α-methoxy-α-(trifluoromethyl)phenyl acetic acid (Mosher's acid)
Na°	sodium metal
$NADP^{+}$	nicotinamide adenine dinucleotide phosphate (oxidized form)
NADPH	nicotinamide adenine dinucleotide phosphate (reduced form)
NaOMe	sodium methoxide
NBS	N-bromosuccinimide
NMP	1-methyl-2-pyrrolidinone
p-NO_2PhCHO	*para*-nitrobenzaldehyde
$Pb(OAc)_4$	lead tetraacetate
PG	peptidoglycan
$PhCH_2NH_2$	benzylamine
PhCHO	benzaldehyde
PhCOCl	benzoyl chloride
Phe	phenyl alanine
$Ph(Et_2N)SO(Me)BF_4$	[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate
PhH	benzene
Ph_3P	triphenylphosphine
$PhSO_3N_3$	phenylsulfonyl azide
PhthNH	phthalimide
PhthNK	potassium phthalimide
PLE	pig liver esterase
PLP	pyridoxal 5-phosphate
PrCHO	butyraldehyde
i-PrCHO	*iso*-butyraldehyde
$(i\text{-Pr})_2NEt$	N,N-diisopropylethylamine (Hünig's Base)
Pyr	pyridine
RaNi	raney nickel
S_N2	bimolecular nucleophilic substitution
Succinyl-CoA	succinyl coenzyme A
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCN	trimethylsilyl cyanide
TsCl	*para*-toluenesulfonyl chloride
TsOH	*para*-toluenesulfonic acid
Tyr	tyrosine
UDP	uridine diphospho

Chapter One

Introduction

1.1 Introduction

The prominence of α-amino acids in nature has provided limitless research opportunities for scientists from such disciplines as chemistry, biology, biochemistry, and medicine. This class of organic molecules is finding increased applications in the fields of asymmetric synthesis, protein engineering, agricultural and food science, and immunology to name just a few. There exists twenty proteinogenic amino acids and in the neighborhood of one thousand naturally-occurring non-proteinogenic amino acids. If one takes into account the numerous examples of unnatural synthetic amino acids, it is quite clear that these molecules occupy an enormous domain in science. For instance, it is now more common than ever to find examples of asymmetric total syntheses in which the initial source and subsequent relay of chirality commences at the α-carbon atom of an amino acid starting material (or synthon). One is also likely to find amino acids or appropriate derivatives utilized as chiral auxiliaries in asymmetric synthesis. Thus, α-amino acids often serve as relatively abundant and inexpensive reagents for multistep chemical syntheses. Recent advances in automated solid support peptide synthesis have allowed for the development of "designer" enzymes and peptide ligands, drug delivery peptides, hormones, immunologically active proteins, as well as a host of other medicinally important peptides. New advances in cellular and molecular biology have intensified the study of protein-DNA interactions, protein-receptor recognition, enzyme activation and mechanisms, as well as other regulatory processes found in nature. Many new inventions, such as biodegradable herbicides and pesticides, have spawned from the creative use of amino acids and peptides as sociopolitical pressures demand a greater awareness for the protection of the global environment. The use of peptides as artificial sweeteners has greatly influenced the food industry and clearly illustrates the profitablility that can be gained from the exploitation of α-amino acids. There is very little question that amino acids will continue to play an important role in future research endeavors.

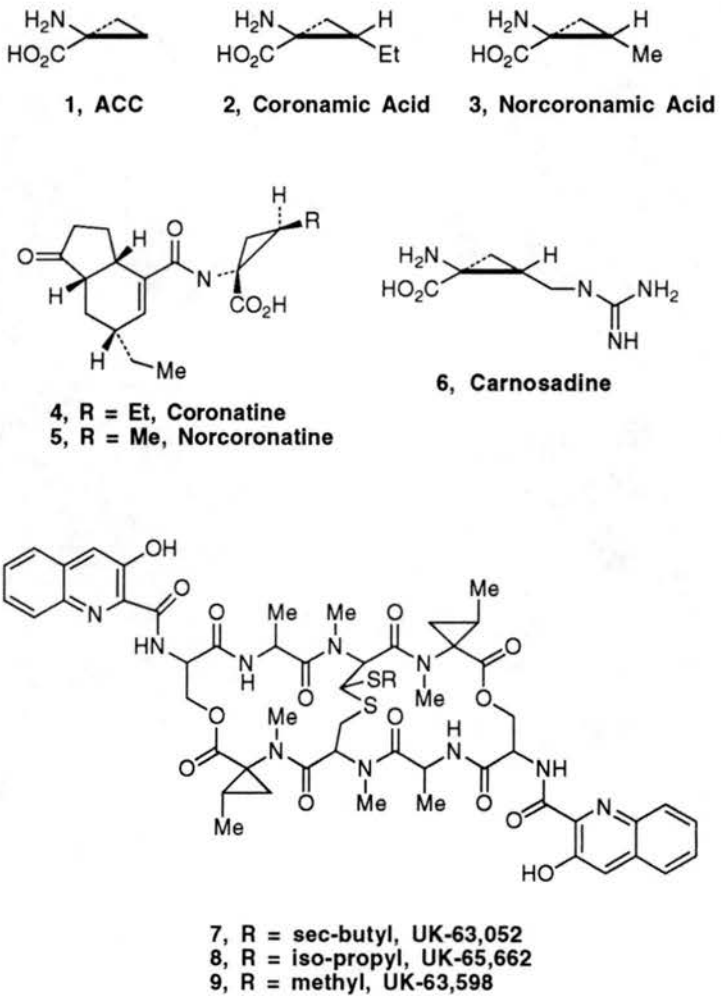
During the last two decades there has been a virtual explosion of technology aimed at the asymmetric syntheses of amino acids of all genres. While many new amino acids are currently being isolated from natural resources (e.g. microbes, plants, and animals) there is a growing need to develop methodology for the synthesis of these compounds, both natural and unnatural. Sometimes this need is governed by the scarcity of natural amino acids. In the latter case, synthetic methodology is driven by the design of amino acids containing previously unkown structural features, possibly as a means to enhance or inhibit biological activity. This facet is no better utilized than in the pharmaceutical industry. For example, as more advances in molecular structure elucidation become available, either through x-ray

analysis or molecular modelling techniques, then the design of unnatural substrates or inhibitors will increase accordingly. This requires that one be able to synthesize proposed structures in an efficient and economical manner. Currently there are numerous synthetic methodologies available for the asymmetric synthesis of α-amino acids, each having a variety of individual strengths and weaknesses. The work described herein involves one such methodology developed for the stereoselective synthesis of amino acids in high optical yield and clearly illustrates various advantages and disadvantages in the approach.

1.2 Biology of Naturally Occurring 1-Aminocyclopropane-1-carboxylic Acids

1-Aminocyclopropane-1-carboxylic (ACC) acid derivatives are a unique, but small class of amino acids found in nature (Figure 1). For example, the parent compound, ACC,

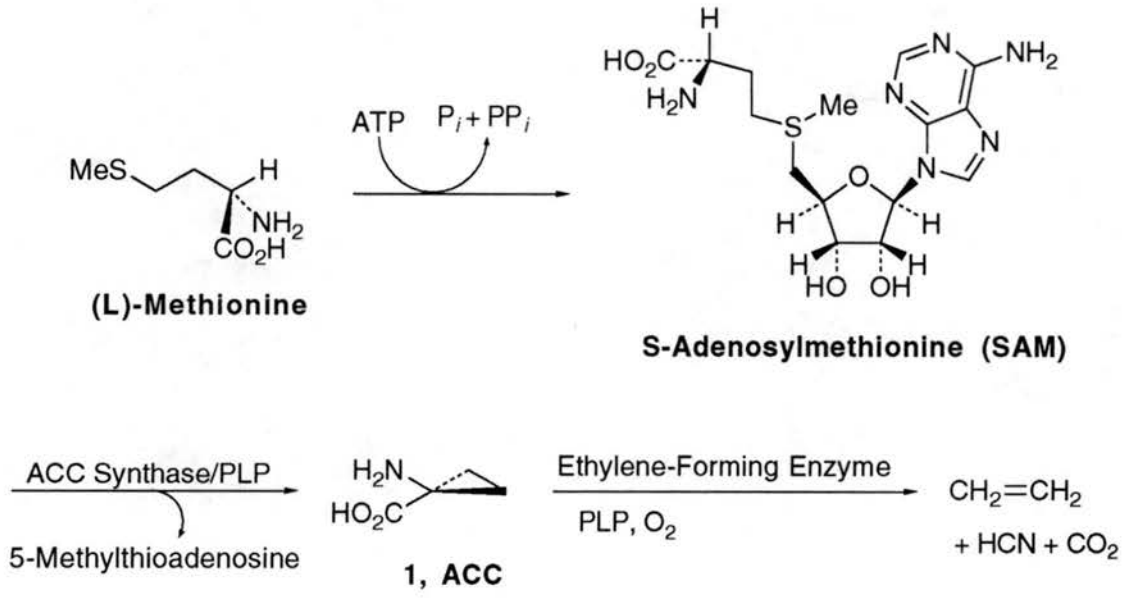
Figure 1



was first isolated from cider apples and perry pears by Burroughs[1a] and from cowberries by Virtanen[1b] in 1957. Interestingly, 1-aminocyclopropane-1-carboxylic acid was first synthesized in 1922, long before its discovery and isolation as a natural product.[1c] Two decades later, (1S,2S)-2-ethyl-1-aminocyclopropane-1-carboxylic acid (**2, coronamic acid**) was isolated from the hydrolysate of coronatine (**4**), a phytotoxin produced by *Pseudomonas coronafacience* var. *atropupurea*.[2] Similarly, (1S,2S)-2-methyl-1-aminocyclopropane-1-carboxylic acid (**3, norcoronamic acid**), has been isolated from norcoronatine (**5**), a minor component of the phytotoxic fractions produced by *Pseudomonas syringae* pv. *glycinea*.[3] In 1984, a novel guanidine-containing ACC, (1S,2S)-carnosadine (**6**), was extracted from the marine red algae *Grateloupia carnosa*.[4] In addition, N-methylated norcoronamic acid of undetermined absolute stereochemistry has been found to be a constituent of the cyclic peptide portion of the newly discovered DNA-intercalating antibiotic UK-63,052 complex (**7-9**) of the quinomycin family, isolated from *Streptomyces braegensis* subsp. *japonicus*.[5]

This family of amino acids is of tremendous interest because of its biological activity and potential use in conformationally restricted peptides and as biosynthetic and mechanistic probes.[6] For example, ACC (**1**) has been determined[7] to be the immediate biosynthetic precursor of ethylene (Scheme 1), the plant hormone responsible for fruit

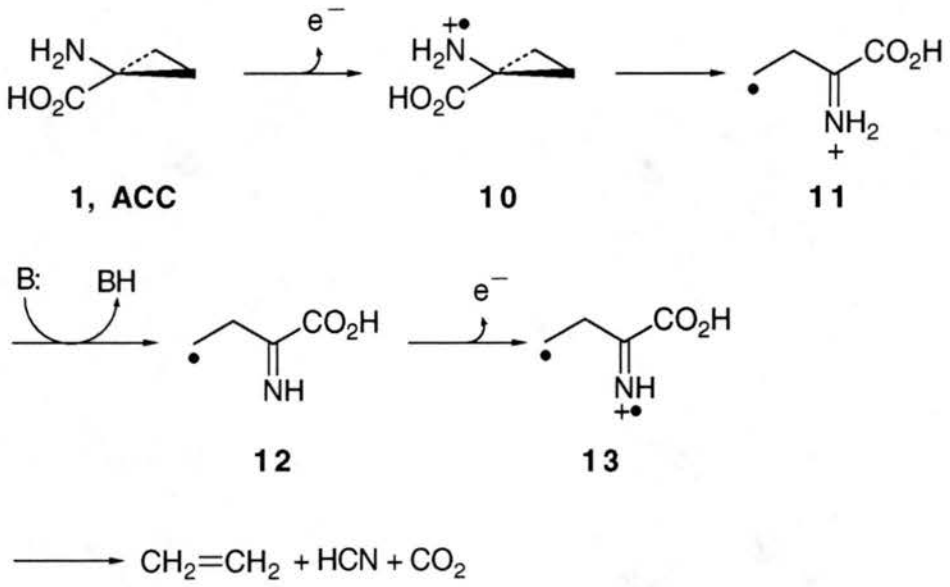
Scheme 1



ripening and which regulates many aspects of plant growth and development.[8] In fact, the connection between ACC and the ripening process was first suggested both by

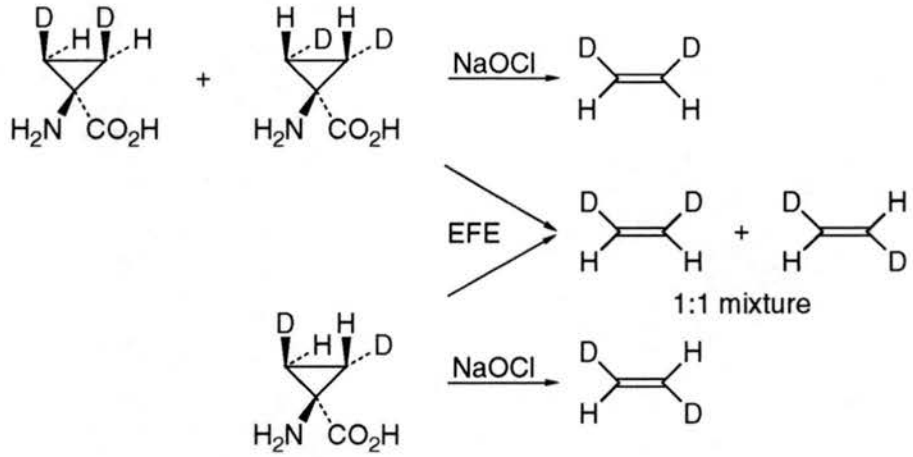
Burroughs[1a] and Virtanen,[1b] where they independently observed elevated concentrations of the cyclopropane amino acid in ripened fruits and berries and virtually no compound in green specimens. The exact mechanism of this biologically significant and commercially important degradation process is as yet unkown, but has come under intense scrutiny.[9] It is believed that the mechanism involves a stepwise oxidative process shown in Scheme 2.

Scheme 2



Single electron oxidation of the nitrogen atom of ACC (**1**) leads to radical cation (**10**) which subsequently undergoes ring opening to give acyclic radical cation intermediate (**11**). Deprotonation of **11** and single electron oxidation of the corresponding radical intermediate (**12**) gives diradical cation **13**. The final step involves homolytic decomposition of **13** to ethylene gas and cyanoformic acid. The precise elucidation of this complex mechanism continues to be hampered by the inability of researchers to isolate and purify the ethylene-forming enzyme (EFE), which is thought to be a membrane-bound protein.[9a] Attempts to isolate EFE free from plant cells has only resulted in denaturation and complete loss of enzymatic activity. Despite the fact that ACC (**1**) is an achiral substrate, stereospecifically-labelled analogues have provided support for this proposed stepwise mechanism. In one study,[9d] racemic *cis*- and *trans*-2,3-dideuterioACCs were prepared and individually incubated with apple tissue, a known source of EFE (Scheme 3). The [$^2H_2$]-labelled ethylene gas formed from these reactions was obtained as a 1:1 mixture of *cis*- and *trans*- isomers. If the formation of ethylene was a concerted process, one would certainly expect *cis*-2,3-[$^2H_2$]-ACC to give *cis*-[$^2H_2$]-ethylene and *trans*-2,3-[$^2H_2$]-

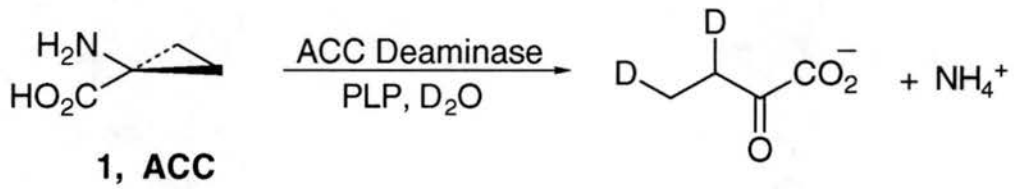
Scheme 3



ACC to give *trans*-[$^2H_2$]-ethylene. This obviously is not the case. Interestingly, the same study showed that treatment of *cis*- and *trans*-2,3-dideuterioACC with NaOCl (aq) gave deuterium-labelled ethylene in which the stereochemistry was retained. The mechanism of degradation for the chemical and enzymatic models is therefore drastically different.

An alternative and highly unusual biological degradation of ACC (**1**) involves the cleavage reaction producing α-ketobutyrate and ammonia (Scheme 4) by ACC deaminase,

Scheme 4



1, ACC

an enzyme isolated from a soil bacterium (*Pseudomonas sp.*) and a yeast (*Hansenula saturnus*).[10] ACC deaminase, purified to homogeneity, is a PLP-containing enzyme known to catalyze the ring opening reaction of ACC (**1**), coronamic acid (**2**),[11] and other monoalkylated ACC derivatives. The proposed mechanism[12] of this complex enzymatic process is shown in Scheme 5. Nucleophilic attack of an undefined basic residue from ACC deaminase on the pro(S) cyclopropyl methylene of the PLP-ACC coenzyme aldimine (**14**) gives the covalent enzyme-ACC complex (**15**). Deprotonation of the pro(R) β-proton by a second basic residue of the active site leads to β,γ-elimination of the enzyme to yield the key intermediate (**16**). Compound (**16**) is thought to undergo protonation at C-4 by the conjugate acid of a third basic enzyme residue situated at the *si* face with respect to the α-

carbon atom (C-2). This enzymatic step provides aldimine intermediate (**17**) which succumbs to hydrolysis, thus regenerating PLP and producing ammonia and α-ketobutyrate. The stereochemical course of this degradation process, although not depicted in Scheme 5, was determined from incubation experiments with stereospecifically labelled analogs of ACC (Figure 2).

Scheme 5

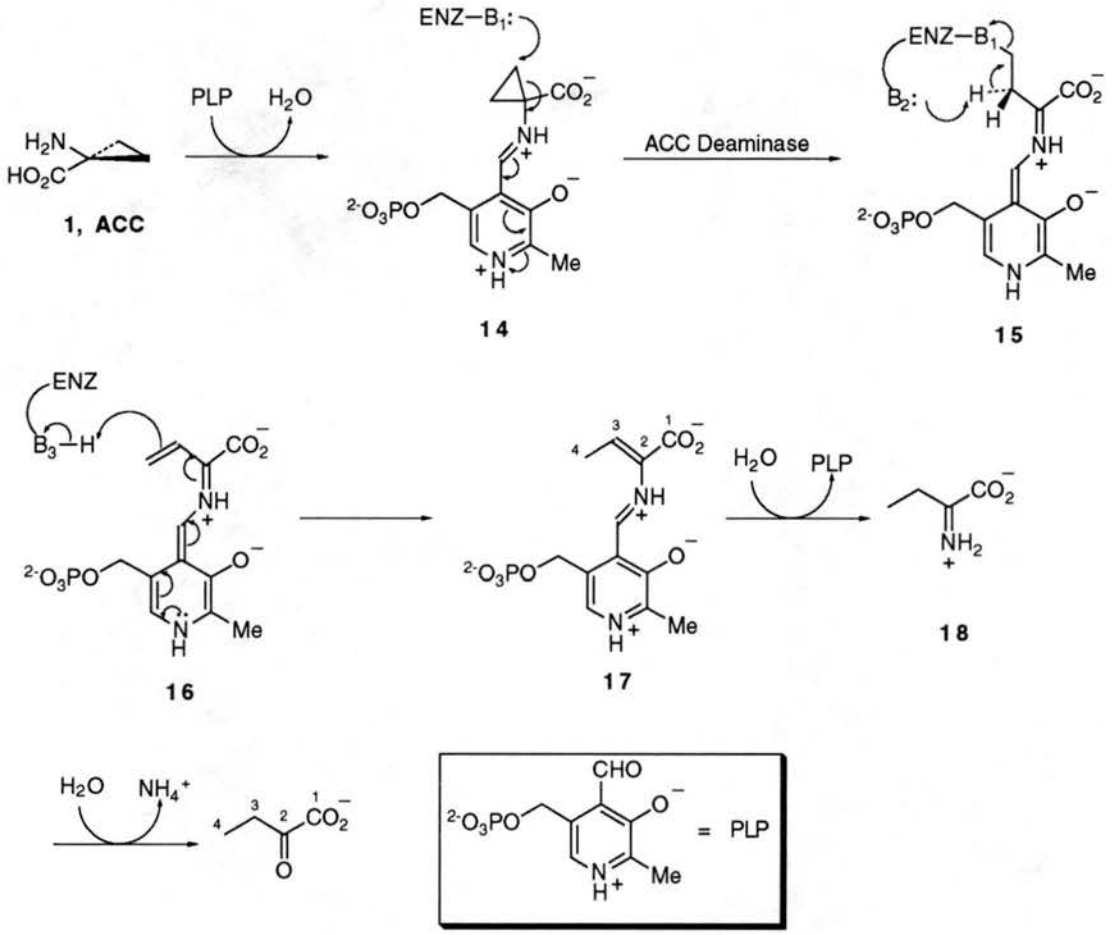
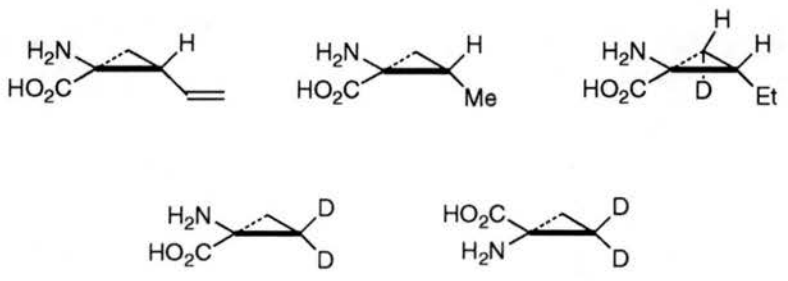


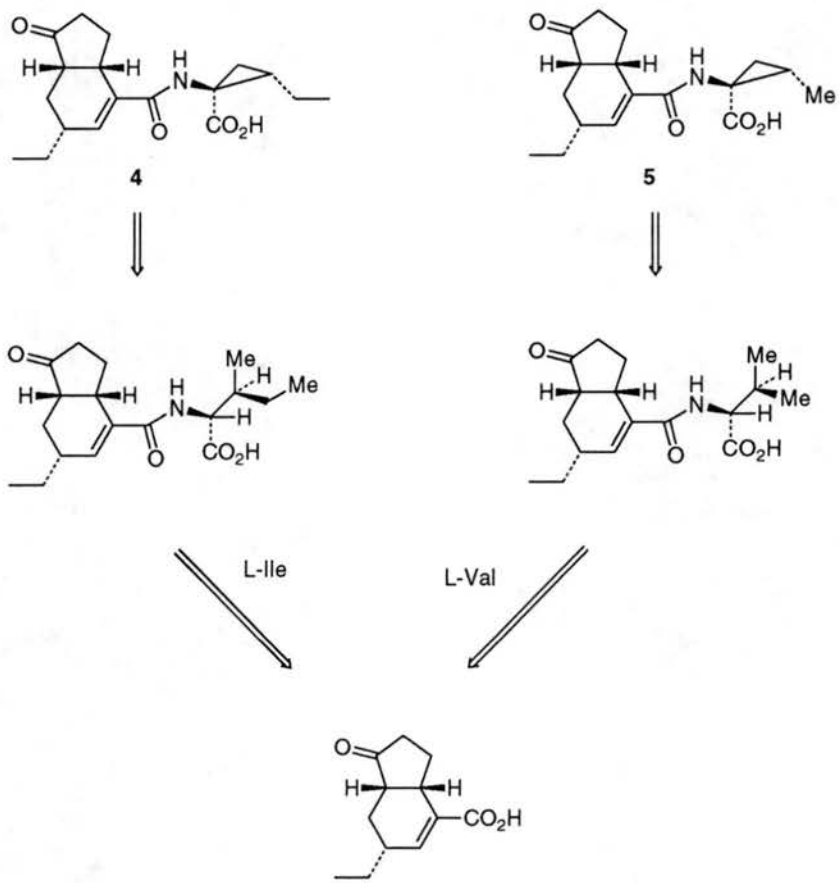
Figure 2



Currently little is known regarding the biology of coronamic acid (**2**), norcoronamic acid (**3**), and carnosadine (**6**). As mentioned earlier, both coronamic and norcoronamic acids are constituents of coronatine (**4**) and norcoronatine (**5**), respectively. These natural products cause chlorosis of Italian ryegrass and soy beans. Chlorosis is a diseased condition of chlorophyll-containing plants in which a yellowing or blanching of green leafy parts by something (e.g. bacteria) other than the lack of light. The mode of action of **4** and **5** remains to be determined. Preliminary studies involving feeding experiments of uniformly ^{14}C-labelled (L)-isoleucine, (L)-threonine, and (L)-valine to cultures of *Pseudomonas syringae* pv. *atropurpurea* and *Pseudomonas syringae* pv. *glycinea* suggest a plausible biosynthetic pathway to natural products **4** and **5** (Scheme 6).

Finally, the biological significance of carnosadine (**6**) as well as the stereochemically undefined norcoronamic acid residues found in the antibiotic UK-63,052 complex (**7-9**) have yet to be determined. However, the discovery of carnosadine, a cyclopropane isostere of (L)-arginine, suggests that "cyclopropylogs" of other proteinogenic α-amino acids may exist in nature.

Scheme 6



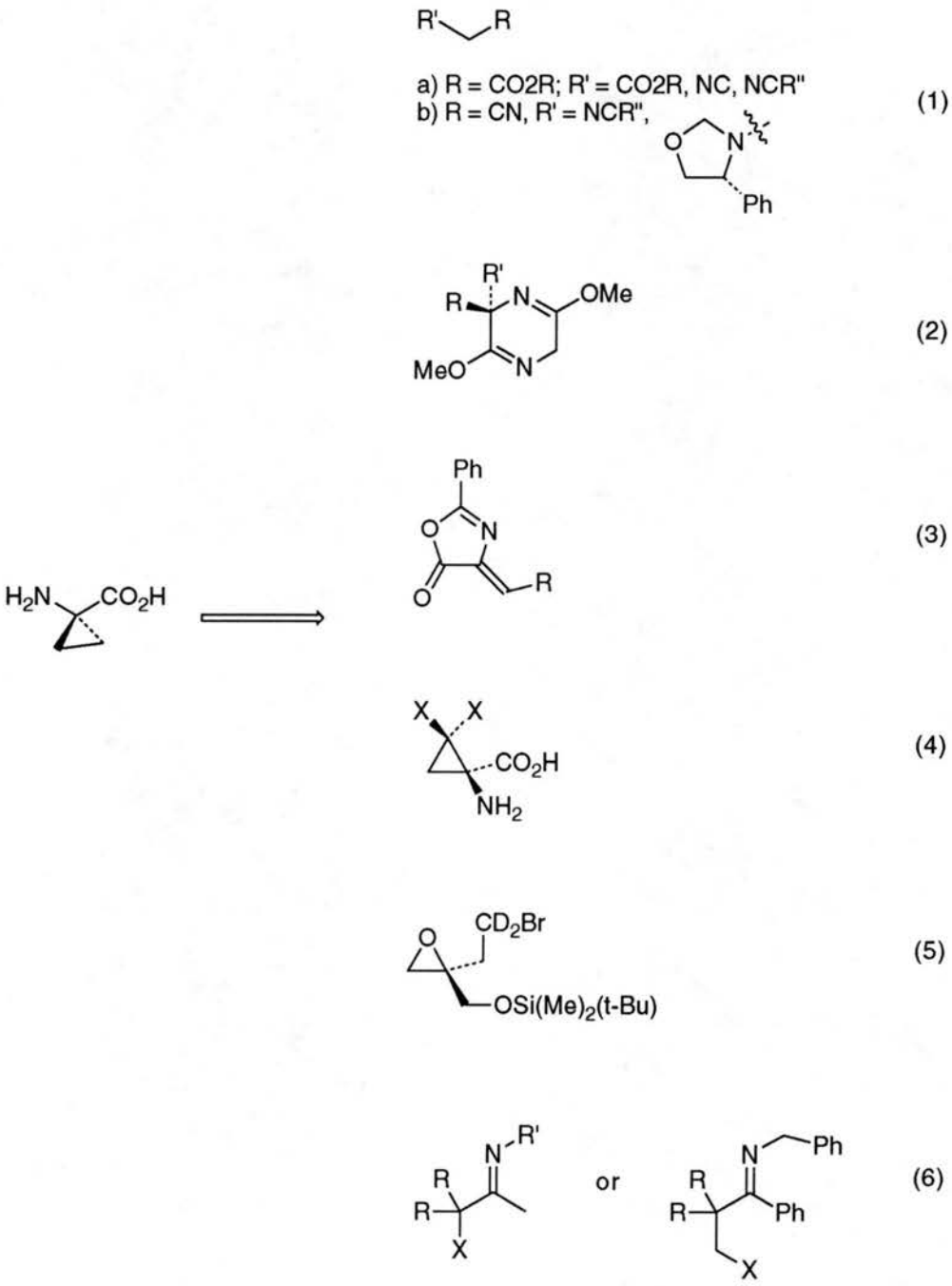
1.3 Asymmetric Syntheses of 1-Aminocyclopropane-1-carboxylic Acids

During the past decade much effort has been directed toward the syntheses of 1-aminocyclopropane-1-carboxylic acid derivatives; some of this work has recently been reviewed.[6,13] Mono- and disubstituted ACCs provide a significant challenge to synthetic chemists due to the difficulty in controlling the relative and absolute stereochemistry about the cyclopropane ring. Existing approaches to the synthesis of this class of amino acids shown in Figure 3, generally involve the following: (1) tandem dialkylation of a glycine equivalent with a 1,2-dibromoalkane or similar 1,2-disubstituted electrophile (eqs 1 and 2);[14] (2) diazoalkane or dimethylsulfoxonium methylide addition to dehydroamino acid derivatives, followed by extrusion of N_2 gas or elimination of DMSO, respectively (eq 3);[15] (3) use of a resolved dihalocyclopropanecarboxylic acid derivative (eq 4);[12b,16] (4) elaboration of chiral, nonracemic epoxide (eq 5);[12b] (5) Lewis acid activated ring opening of a substituted epoxide with a lithiated glycine equivalent followed by subsequent cyclization (eq 1);[17] and (6) cyanide addition to α-chloro ketimines or base-induced cyclization of β-chloroimines (eq 6).[18] All of these approaches have their individual strengths and weakenesses and there is no single, general stereocontrolled approach to differentially substituted ACC derivatives in optically pure form. Most of the available syntheses of 2-substituted ACC derivatives are racemic by design, can involve lengthy procedures, and often incorporate enzymatic or chemical resolutions as the final step. To date there exists only eleven asymmetric and three stereocontrolled syntheses of the title amino acids, and there are no known protocols in which a chiral cyclopropanating reagent has been used to synthesize these compounds. The remainder of this section will be devoted to a review of only the asymmetric and stereocontrolled syntheses of ACC derivatives that are currently available. As mentioned earlier, some of these syntheses are already reviewed,[6,13] however there have been a few very recent contributions. This brief review should serve as a means for the reader to compare and contrast existing methodology with that developed in these laboratories and described later in Chapter 2.

The first asymmetric synthesis of a 1-aminocyclopropane-1-carboxylic acid (ACC) derivative was reported in 1984 by Arigoni and coworkers[12b] whereby they stereoselectively incorporated two deuterium atoms onto one enantiotopic carbon atom of the achiral 1-aminocyclopropane-1-carboxylic acid. The synthesis began (Scheme 7) with the $LiAlD_4$ reduction of 3-methyl-3-butenoic acid (**19**) to afford, after acetylation, alcohol **20** , thus establishing the deuteriomethylene group. Allylic oxidation of **20** using SeO_2 and *tert*-butyl hydroperoxide furnished a mixture of regioisomeric allylic alcohols **21a** and **21b** which were separable by chromatography. The first of two key reactions in the

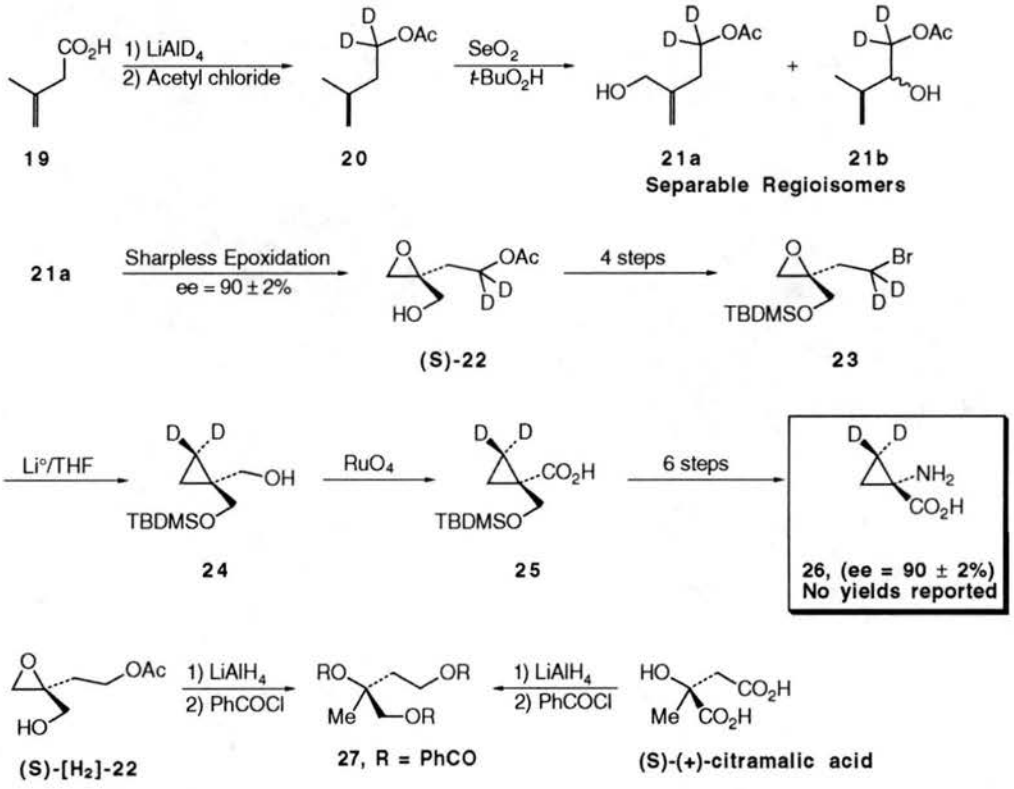
synthesis involved the Sharpless epoxidation[19] of **21a** to give (S)-epoxide **22**. Reduction of an unlabeled sample of **22** with $LiAlH_4$ followed by acylation with benzoyl chloride gave the tribenzoate **27**, $[\alpha]_D = +9.14°$ ($CHCl_3$). Tribenzoate **27**, $[\alpha]_D = +10.23°$ ($CHCl_3$), has been synthesized independently from (S)-(+)-citramalic acid[20] and thus confirmed epoxide **22** to have the *S* configuration with an enantiomeric purity estimated to

Figure 3

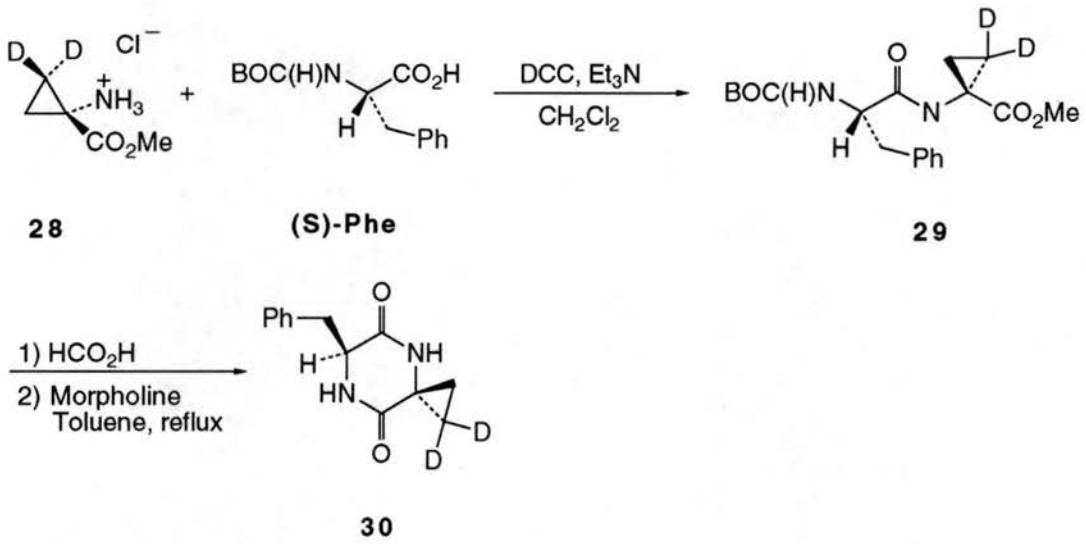


be 90 ± 2%. A standard four step functional group manipulation of **22** provided bromide **23**, the key intermediate for the conversion of the epoxide functionality into the corresponding cyclopropane ring. Thus metal-halogen exchange of **23** with lithium metal followed by subsequent attack of the newly generated carbanion on the epoxide ring via an intramolecular S_N2 displacement provided deuterium labelled cyclopropane **24**. Oxidation of the unprotected hydroxymethyl group of **24** to carboxylic acid **25**, followed by Curtius rearrangement and routine functional group manipulation led to the final synthesis of (R)-1-amino[2,2-$^2H_2$]cyclopropane-1-carboxylic acid (**26**). The enantiomeric purity was assessed independently by converting (R)- and (S)-phenylalanine into diketopiperazine **30** (Scheme 8). The ^1H NMR (taken in $CF_3CO_2{}^2H$) of **30** displayed two sharp doublets at δ0.33 and δ0.71(J = 5.1 Hz) and a second set of doublets with less than 5% intensity at δ0.95 and δ1.45. The upfield set of doublets represents cyclopropane protons which are shielded by the phenyl ring of **30**. It has been demonstrated by Bose and coworkers[21] that cyclic dipeptides containing aromatic amino acid residues adopt a boat conformation about the six-membered ring and a "folded conformation" for the aromatic side chain. Thus, it was concluded that the stereocenter of **26** is of the *R* configuration and the enantiomeric excess to be approximately 90 per cent.

Scheme 7

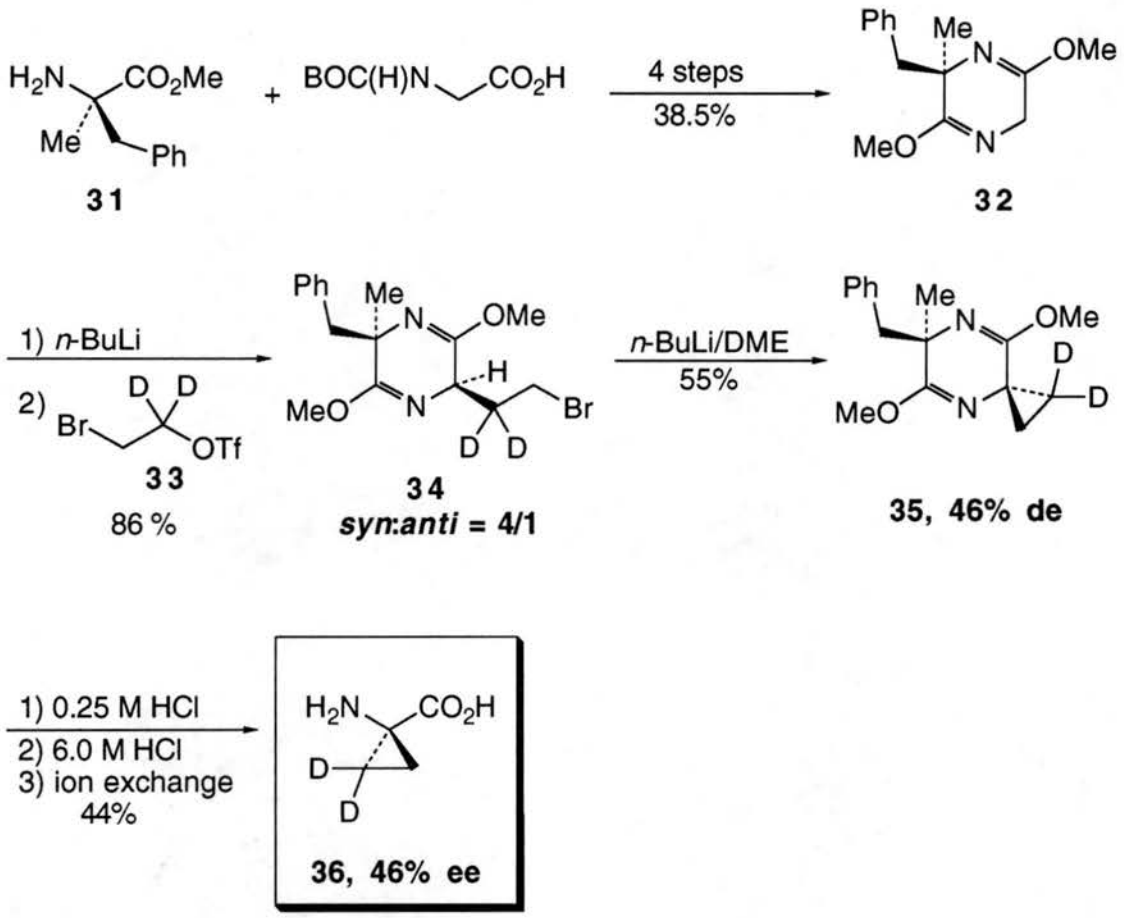


Scheme 8



Woodard and coworkers[14h] have prepared both enantiomers of $^2H_2$-ACC via the well known Schöllkopf bis(lactim ether) methodology,[22] which allows for the direct assessment of %ee of the corresponding amino acid. The synthesis began with the cyclocondensation of (R)-(+)-2-methyl-3-phenylalanine, methyl ester (**31**)[23] with N-*t*-BOCglycine[24] to form the corresponding 2,5-diketopiperazine in three steps(Scheme 9). Treatment of the diketopiperazine with trimethyloxonium tetraflouroborate afforded bis(lactim ether) **32** in 38.5% overall yield. Metallation of **32** by *n*-BuLi (1 equiv in THF) at -78 °C followed by alkylation with 2-bromo[1,1-$^2H_2$]ethyl triflate (**33**) afforded bis(lactim ether) **34** as a mixture of *syn*- and *anti*-diastereomers (4:1)[25] in 86% yield. Despite this unusual violation of the Schöllkopf rule (i.e. alkylation from the more hindered face of the bis(lactim ether)), the *syn*- and *anti*-diastereomers of **34** were not separated since treatment with *n*-BuLi converted the newly alkylated α-center from sp^3 hybridization to sp^2 hybridization and all stereochemical information was lost. Thus treatment of bis(lactim ether) **34** with *n*-BuLi (1 equiv in THF) at -78 °C followed by intramolecular S_N2 ring closure gave cyclopropane **35** as a mixture of *syn*- and *anti*-diastereomers in a 2.7:1 ratio, again the unexpected *anti*-Schöllkopf addition. The *S* configuration at the spirocyclopropane carbon atom was assigned by ^1H NMR, as the methylene hydrogen atoms are located within the shielding cone of the aromatic ring (benzyl group) and experience an upfield shift of Δδ 0.6 ppm relative to the methylene protons of the minor diastereomer.

Scheme 9

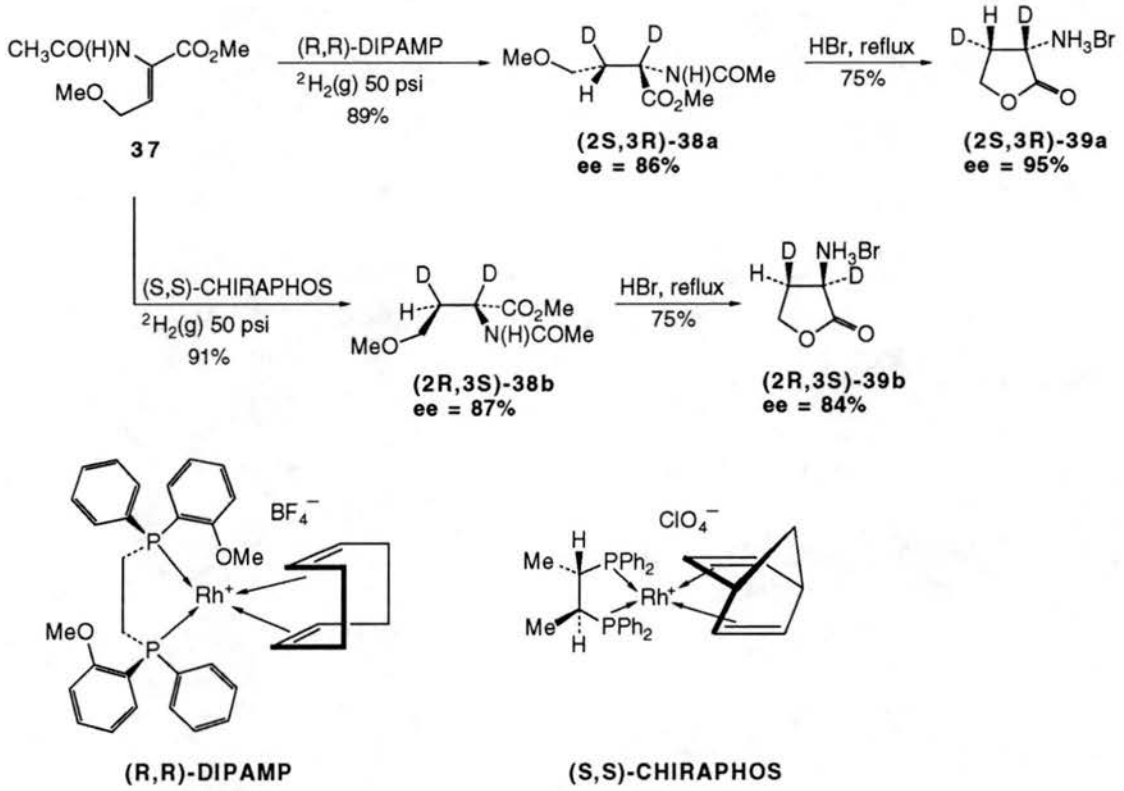


The synthesis of $^2H_2$-ACC was accomplished by a two step hydrolysis of **35**; first with 0.25 N HCl for 48 hours, followed by refluxing 6 N HCl for one hour. The first hydrolysis reaction produces **31·HCl** and methyl 1-amino[2,2-$^2H_2$]cyclopropane-1-carboxylate as a 2.7:1 mixture of enantiomers. The final hydrolysis reaction, albeit rather harsh, furnishes the corresponding amino acid hydrochloride salts which were eluted with 1 N NH_4OH on cation exchange resin and separated by preparative thin layer chromatography. In this manner (S)-[$^2H_2$]-ACC (**26**)was obtained in 44% yield and an enantiomeric excess of 46%. The (R)-isomer of **26** can be obtained as the major enantiomer if one substitutes triflate **33** with regioisomeric 2-bromo-2,2-dideuterioethyl triflate during the initial alkylation step of the synthesis.

Woodard and associates[14k] have also accomplished the asymmetric synthesis of stereospecifically monodeuteriated ACC's, (1S,2R)- and (1S,2S)-1-amino[2-^2H]-cyclopropane-1-carboxylic acids, based again in part on the Schöllkopf method.[22] The synthesis began with the preparation of (2S,3R)-[2,3-$^2H_2$]- and (2R,3S)-[2,3-

$^2H_2$]homoserine lactones **39a** and **39b** (Scheme 10). Using the protocol of Scott and coworkers,[26] methyl (Z)-2-acetamido-4-methoxybut-2-enoate (**37**) was reduced with $^2H_2$ gas in the presence of either (R,R)-DIPAMP or (S,S)-CHIRAPHOS catalysts to furnish

Scheme 10



(R,R)-DIPAMP

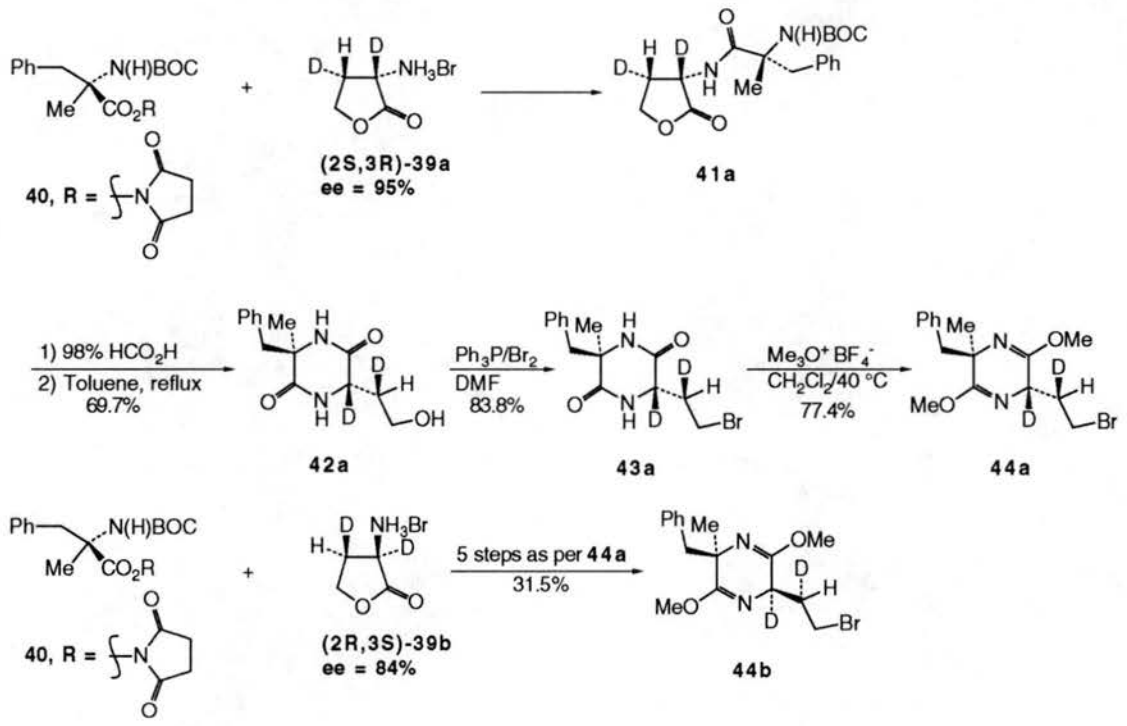
(S,S)-CHIRAPHOS

either (2S,3R)-N-acetyl-O-methyl[2,3-$^2H_2$]homoserine methyl ester (**38a**) or (2R,3S)-N-acetyl-O-methyl[2,3-$^2H_2$]homoserine methyl ester (**38b**), respectively. Compound **38a** was obtained in 89% yield and an enantiomeric excess of 86% and **38b** was obtained in 91% yield and an 87% ee. Since catalytic reductions of this genre proceed by *cis* addition of hydrogen (in this case deuterium) to the alkene, then the new stereocenter at carbon atom 3 of either **38a** or **38b** should have an identical enantiomeric purity to that at the asymmetric α-amino acid carbon atom. Derivatives **38a** and **38b** were both independently refluxed with 48% HBr (aq) to give in 75% yield **39a** and **39b** with enantiomeric excesses at the α-carbon of 95% and 84%, respectively.

The next phase of the synthesis involved converting lactones **39a** and **39b** into bis(lactim ethers) **44a** and **44b** (Scheme 11). Lactones **39a** and **39b** were coupled to the hydroxysuccinimide ester[27] of (2R)-N-*t*-BOC-2-methyl-3-phenylalanine (**40**)[23] to give protected dipeptide lactones **41a** and **41b**, which were subsequently cyclized in an

intramolecular fashion to produce diketopiperazines **42a** and **42b** in 69% yield. Diketopiperazines **42a** and **42b** were converted to the corresponding bromides **43a/43b** by the treatment of Ph_3P/Br_2[28] and then to the bis(lactim ethers) **44a** and **44b** in the usual

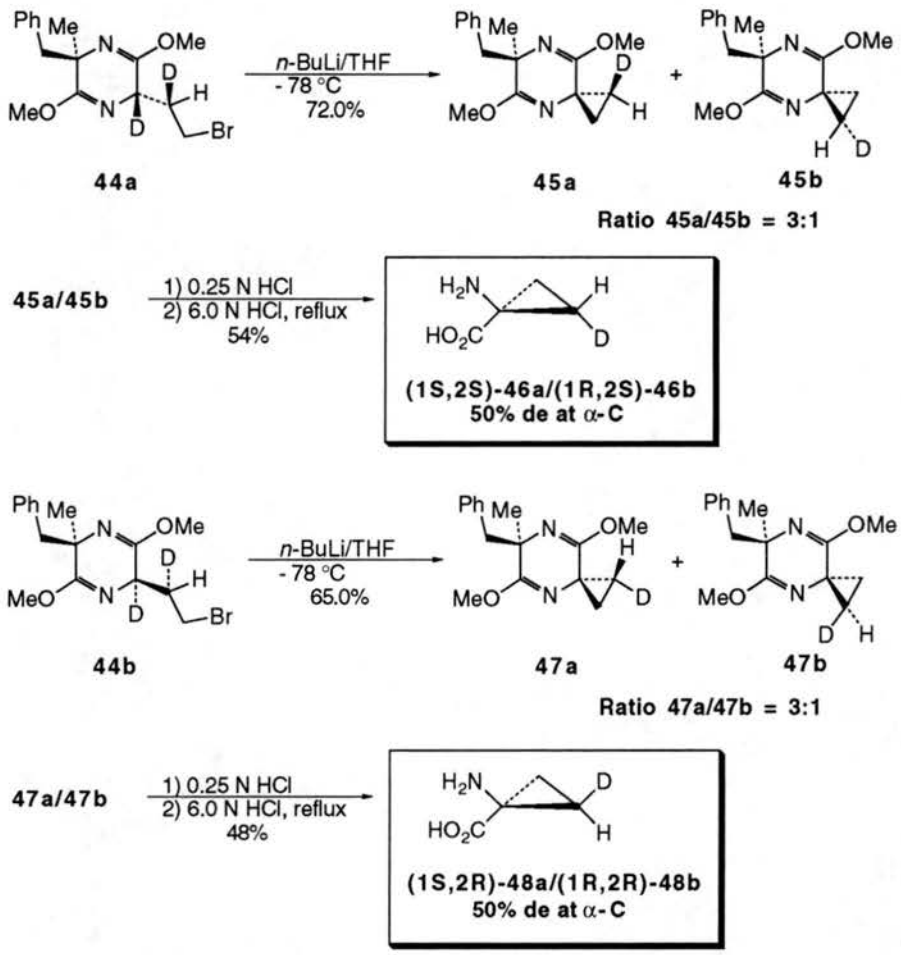
Scheme 11



way. Independent treatment of **44a** and **44b** with *n*-BuLi at - 78 °C effected an intramolecular cyclization (Scheme 12) to give predominantly the bis(lactim ether) cyclopropane diastereomers **45a** and **47a**, respectively (**45a/45b** = **47a/47b** = 3/1). The ratios and configurational assignments for **45** and **47** were determined from high field ^1H NMR analysis. It should be noted that the authors do not account for the two additional minor cyclopropane diastereomers of **45** and **47**, which are derived from the stereochemically impure lactones **39a** and **39b**. Conversion of **45a/45b** and **47a/47b** to the 2-[^2H]ACCs **46a** and **48a** was accomplished by the two step acid hydrolysis sequence as described earlier for the [$^2H_2$]ACC synthesis.[14h] The target (1S,2S)- and (1S,2R)-1-amino[2-^2H]cyclopropane-1-carboxylic acids (**46a** and **48a**, 50% de at C-1) were separated from the chiral auxiliary reagent (2R)-2-methyl-3-phenylalanine by preparative thin layer chromatography. Schöllkopf and coworkers[29] used the bis(lactim ether) methodology to generate chiral, non-racemic electophilic carbenes for the aymmetric synthesis of novel 1-amino-2-arylcyclopropene-1-carboxylic acids in high enantiomeric excess (Scheme 13). Bis(lactim ether) **49**[30] was lithiated at - 78 °C with *n*-BuLi in THF

and then diazotized by treatment with benzenesulfonyl azide. The diazo derivative of **49** was converted *in situ* to carbene intermediate **50**[31] by the addition of one equivalent of *n*-BuLi. After 10 minutes, the resulting mixture was added through a Teflon tube to neat

Scheme 12

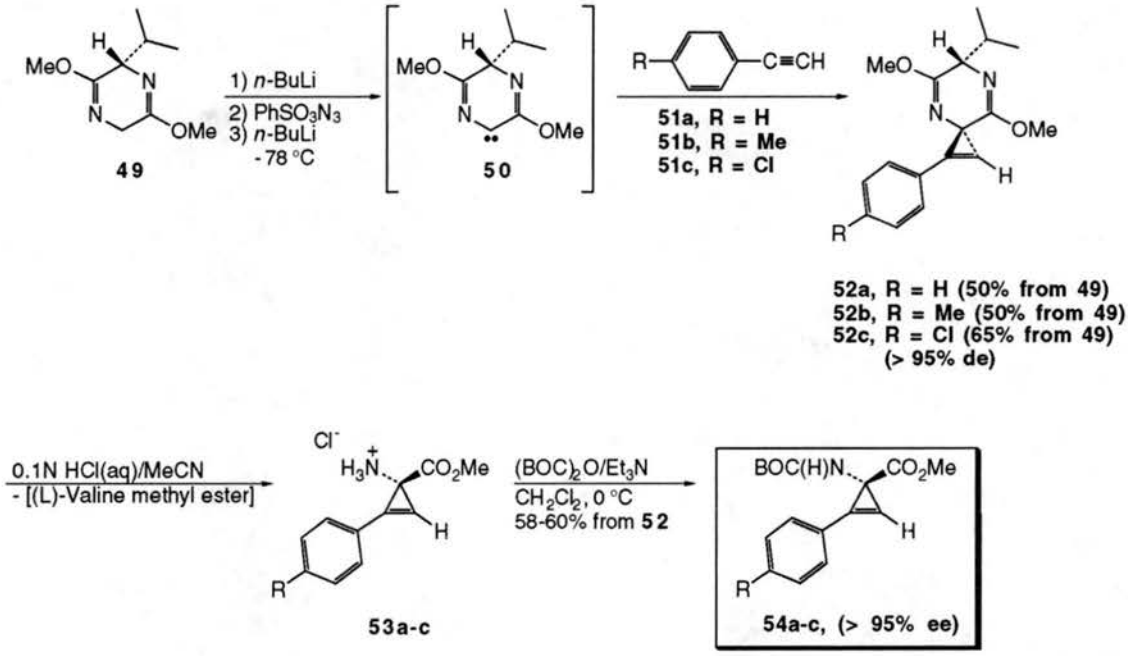


aryl acetylenes **51a-c**, providing bis(lactim ether) cyclopropanes **52a** and **52b** in 50% yield and **52c** in 65% yield. The addition occurs stereospecifically giving the *anti*-isomers as evidenced by single crystal x-ray analysis of carbene adduct **52a**. Hydrolysis of **52a-c** with dilute HCl, followed by acylation of the nitrogen atom of **53a-c** with di-*tert*-butyldicarbonate furnished the diprotected cyclopropene amino acids **54a-c** (60%) in greater than 95% ee.

The first asymmetric synthesis of (-)-(1S,2R)-allocoronamic acid was reported by Marco[14i] in which phenylglycinol serves as a chiral auxiliary for the preparation of chiral, non-racemic α-amino nitriles, first described by Husson and coworkers.[32] The synthesis (Scheme 14) began with the dialkylation of oxazolidinone **55** with racemic epibromohydrin

to produce cyclopropane **56** as a mixture of four possible diastereomers which were not separated. Hydrolysis of the nitrile and aminal functions of **56** with refluxing NaOH and dilute HCl, followed by esterification ($SOCl_2$/MeOH) gave an inseparable mixture of *cis*-

Scheme 13

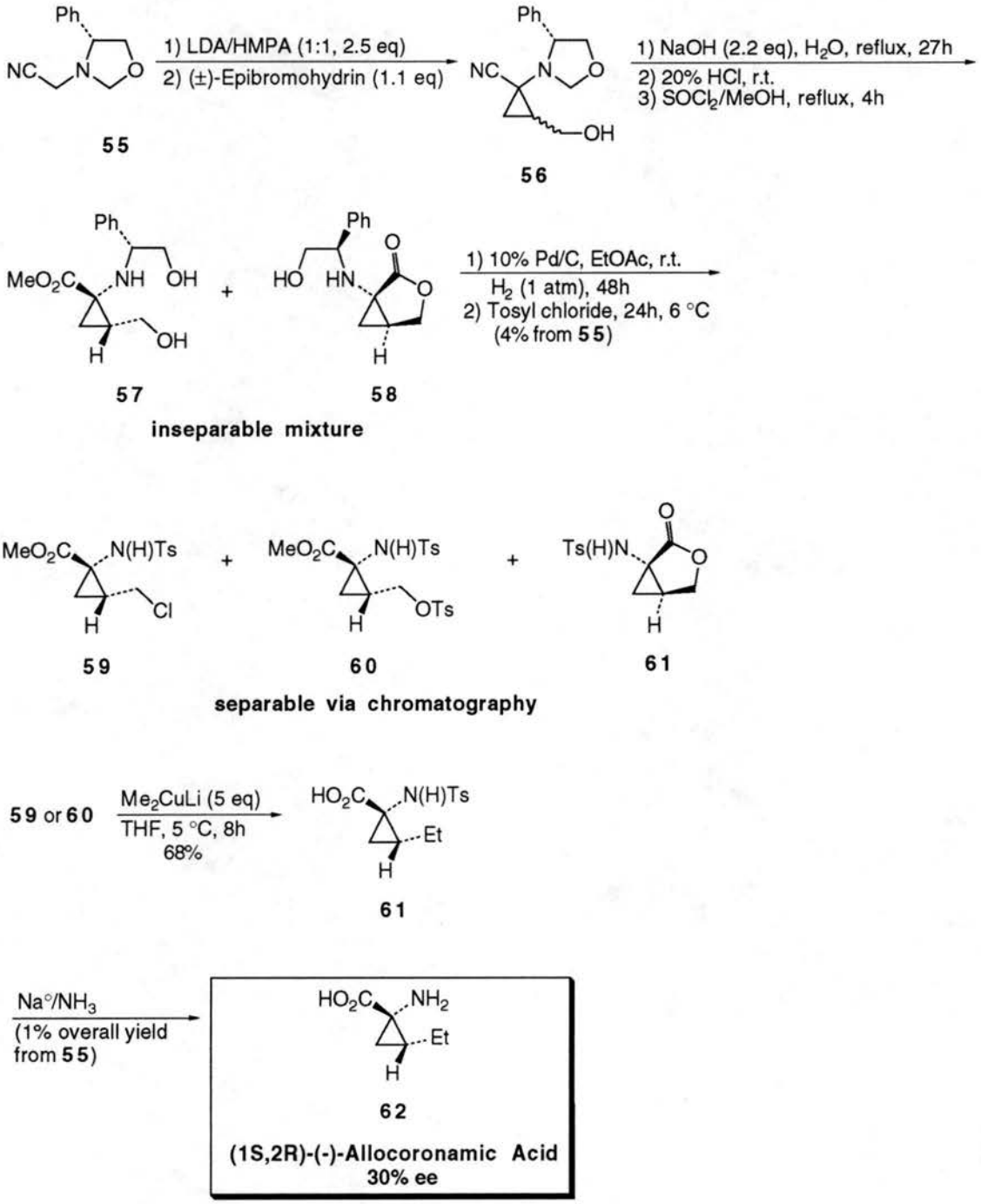


cyclopropane **57** and *trans*-cyclopropane **58**, which spontaneously lactonized under the reaction conditions. Hydrogenolytic cleavage of the chiral auxiliary and tosylation of the corresponding free amines produced a separable mixture of *cis*-cyclopropanes **59** and **60** in additon to *trans*-cyclopropane **61**. Treatment of either **59** or **60** with lithium dimethylcuprate followed by reductive detosylation of **62** afforded (1S,2R)-(-)-allocoronamic acid (**63**) in 1% overall yield from **55** and 30% ee. The poor stereoselectivity in the cyclopropane-forming reaction of this sequence reflects the difficulties associated with acyclic, non-chelation controlled enolate reactions in general.

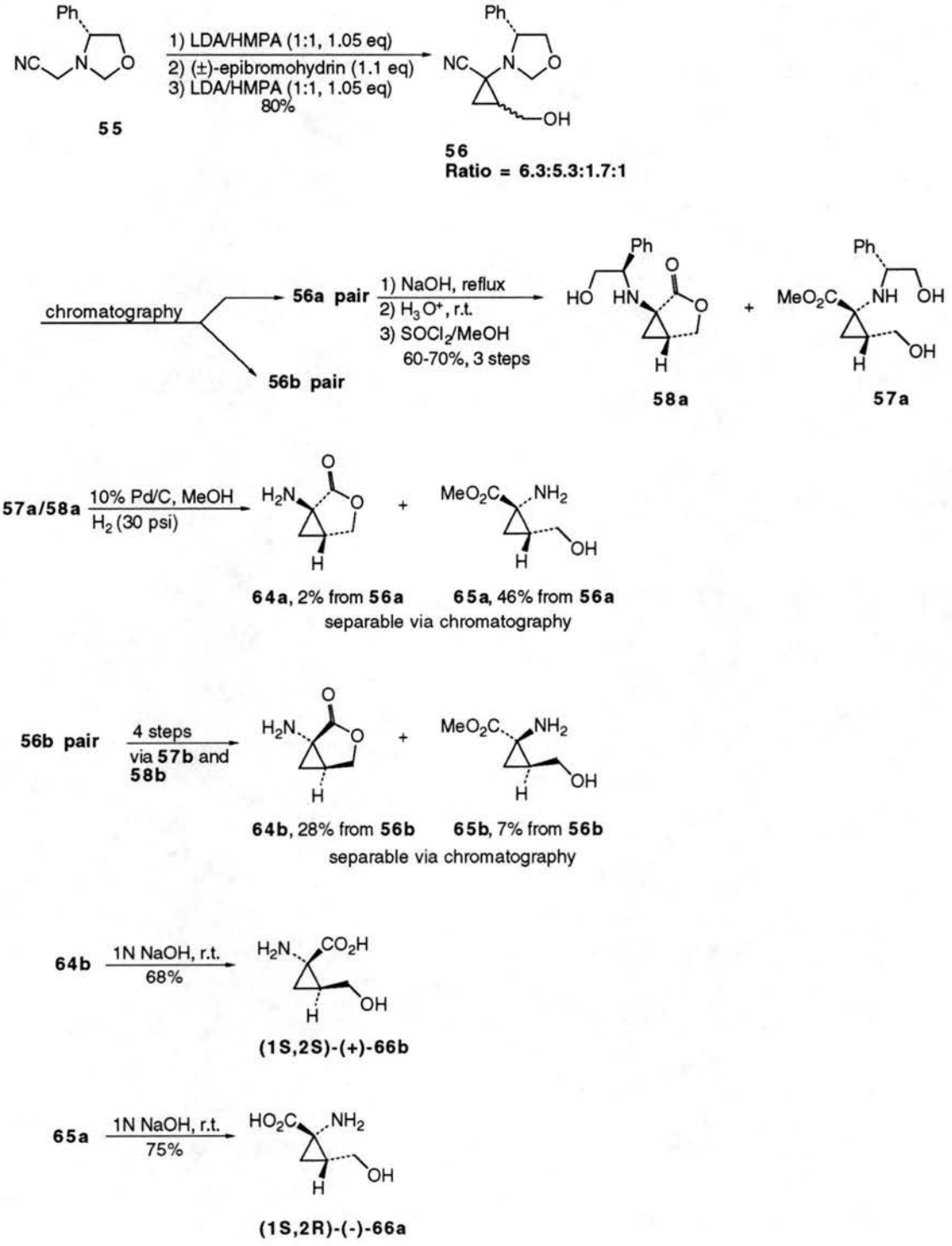
Following the report by Marco,[14i] Husson and associates[14j] described a synthesis of all four possible diastereomers of 1-amino-2-(hydroxymethyl)cyclopropane-1-carboxylic acid from the same chiral, non-racemic oxazolidinone **55** (Scheme 15). Cycloalkylation of **55** with racemic epibromohydrin not surprisingly gave all four possible diastereomers of **56**, which in this study were tediously separated into two pairs, each consisting of one major and one minor diastereomer (in a ratio of 85:15 for both pairs). The major isomer of the first pair has a *cis*-relationship between the nitrile and hydroxymethyl substituents while that of the second pair had a *trans*-relationship between the two substituents. Each

diastereomeric pair of **56** was treated sequentially with refluxing NaOH, dilute HCl, and thionyl chloride/MeOH to afford two pairs of diastereomeric **57** and **58**. During the esterification reaction of the three step sequence, cyclopropanes with the *cis* -orientation undergo spontaneous lactonization giving compounds **58**, while those with the *trans* arrangement yield cyclopropane methyl esters **57**. The chiral auxiliary of each **57/58** pair

Scheme 14



Scheme 15

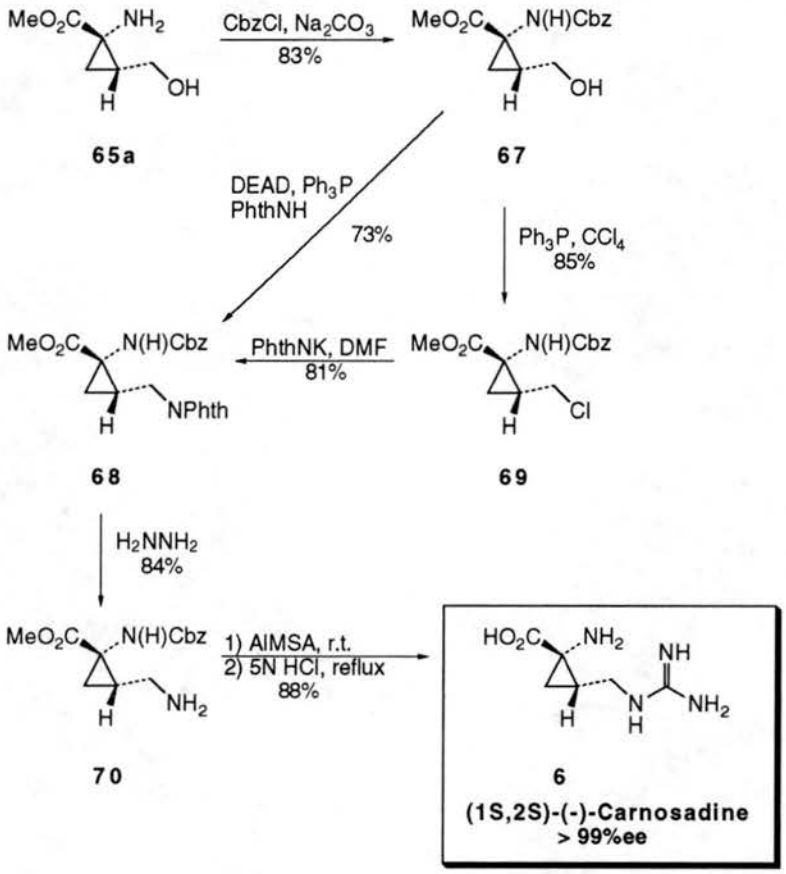


was removed by hydrogenolysis followed by chromatographic separation of the major diastereomer from each pair. Thus, the major diastereomer of **58** gave optically pure

(1S,2S)-(+)-lactone (**64b**) in 28% overall yield and the major diastereomer of **57** gave optically pure (1S,2R)-(-)-methyl 1-amino-2-(hydroxymethyl)cyclopropane-1-carboxylic acid (**65a**) in 46% overall yield. In a follow-up full paper by the Husson group,[14m] compounds **64b** and **65a** were each individually saponified to the corresponding free amino acids **66b** and **66a** in 68% and 75% yields, respectively. Again, the major criticism to this methodology lies in the stereorandom nature of the cycloalkylation reaction to form compound **56**.

The most recent application of the chiral, non-racemic α-aminonitrile methodology was reported by Husson and coworkers[33] in the asymmetric synthesis of (1S,2S)-(-)-carnosadine (**6**) (Scheme 16). The synthesis utilized optically pure (1S,2R)-(-)-methyl 1-

Scheme 16

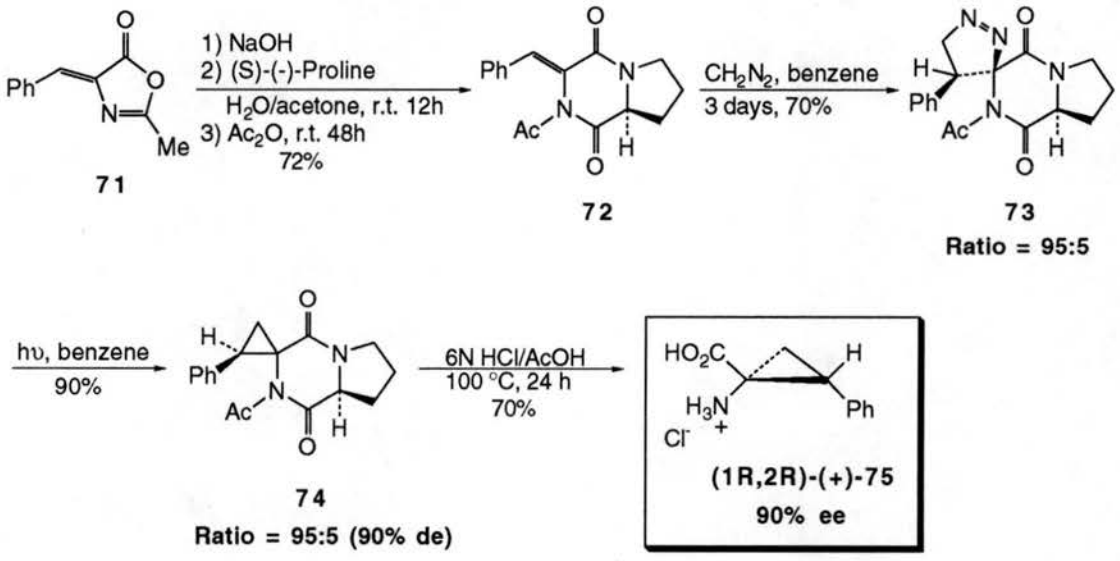


amino-2-(hydroxymethyl)cyclopropane-1-carboxylate (**65a**, Scheme 15)[14j] as the starting material. Compound **65a** was first protected as the carbamate by reaction with benzyl chloroformate to give **67** in 83% yield. Conversion of the primary hydroxyl function to an amino group was achieved by two possible routes. Reaction of **67** with phthalimide in a Mitsunobu procedure furnished the phthalimido derivative **68** in 73% yield. The

alternative procedure involved treatment of **67** with a refluxing mixture of triphenylphosphine and CCl_4, followed by nucleophilic displacement of chloride with potassium phthalimide in DMF, thus providing **69** in 69% yield for the two steps. Despite the slightly lower yield, the latter procedure was preferred because of the ease of purification. The authors also attempted to directly convert chloride **69** into the title compound by the treatment of a methanolic guanidine solution; however this method failed. Nevertheless, hydrazinolysis of **68** provided amine **70** in 84% yield. Finally, treatment of free amine **70** with one equivalent of aminoiminomethanesulfonic acid (AIMSA)[34] in methanol, followed the acidic removal of the benzyloxycarbonyl protection, afforded diastereomerically pure (1S,2S)-(-)-carnosadine (**6**) in 88% yield after ion-exchange chromatography.

Bernabé and coworkers[15q] have reported the first asymmetric synthesis of (1R,2R)- and (1S,2S)-1-amino-2-phenylcyclopropane-1-carboxylic acids ((Z)-cyclopropylPhe). The synthesis (Scheme 17) of the (1R,2R)-diastereomer began with the condensation of (Z)-2-

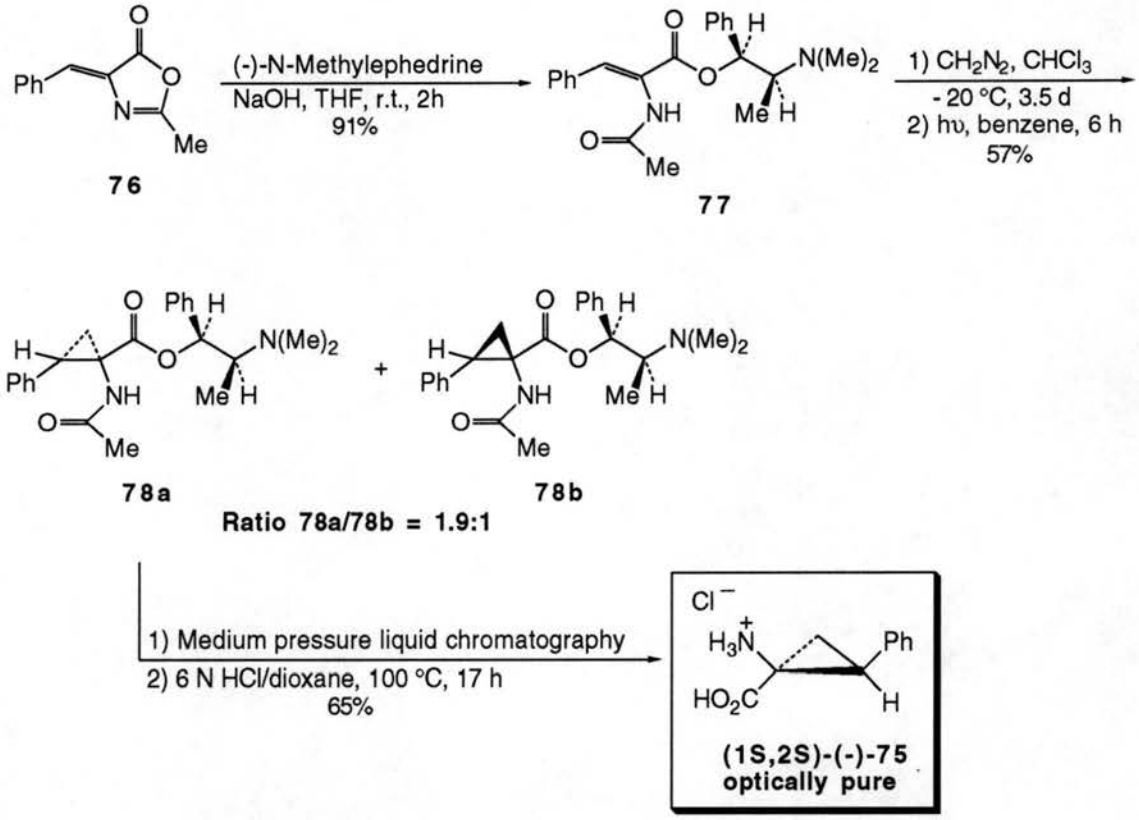
Scheme 17



methyl-4-benzylideneoxazolone (**71**) and (L)-proline, followed by N-acylation with Ac_2O to give diketopiperazine **72** in 72%. Reaction of **72** with diazomethane gave pyrazoline **73** in 70% yield as a 95:5 mixture of diastereomers in which addition to the *si* face predominated; the reason for this unusually high diastereofacial selectivity was not disclosed by the authors. Photolysis of **73** in benzene and hydrolysis of the resulting cyclopropane derivative **74** provided (1R,2R)-(+)-cyclopropylPhe (**75**) in 63% yield and 90% ee.

The synthesis of the enantiomer of **75** was accomplished via the agency of (-)-N-methylephedrine as chiral auxiliary (Scheme 18). (Z)-2-phenyl-4-benzylideneoxazolone (**76**) was condensed with (-)-N-methylephedrine to afford chiral non-racemic ester **77** in

Scheme 18

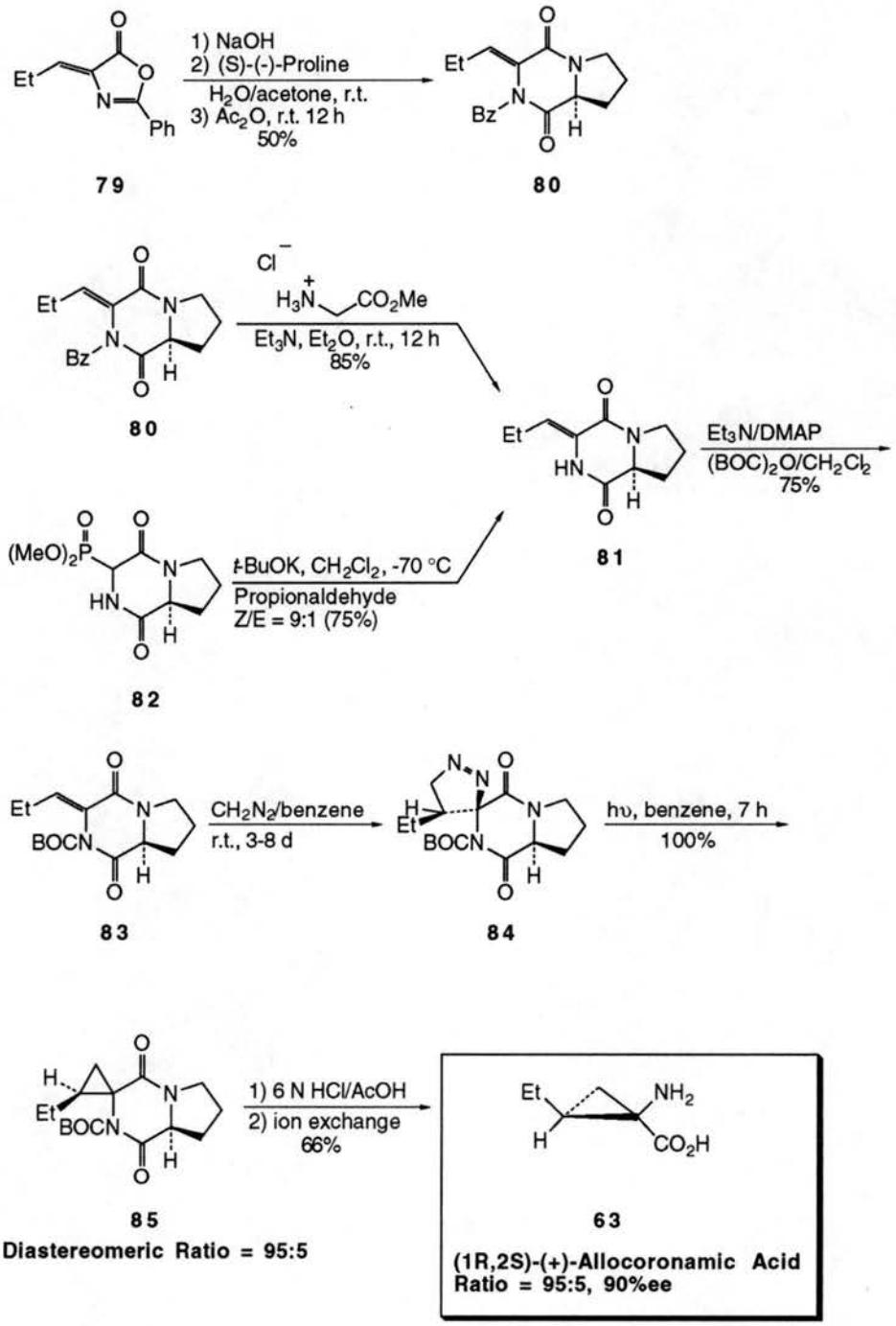


91% yield. Treatment of **77** with CH_2N_2 at - 20 °C followed by photolysis of the corresponding pyrazoline mixture gave cyclopropane diastereomers **78a** and **78b** in 57% yield and a 1.9:1 ratio. Diastereomer **78a** was separated by medium pressure liquid chromatography and hydrolyzed to optically pure (1S,2S)-(-)-**75** in 65% yield. Some questions have been raised about the stabilities of (-)- and (+)-**75** to such harsh hydrolysis conditions.

In an analogous fashion, the Bernabé group[15t] has synthesized (1R,2S)-(+)-allocoronamic acid via the same strategy employed for the (Z)-cyclopropylPhe synthesis.[15q] As shown in Scheme 19, diketopiperazine (**80**) was synthesized from (Z)-2-phenyl-4-propylidene-5(4H)-oxazolone (**79**)[35] and (S)-(-)-proline using the Schmidt protocol.[36] Addition of CH_2N_2 to **80** followed by photolysis of the corresponding pyrazoline failed to provide the desired cyclopropane derivative. Based on previous unpublished results, Bernabé and coworkers opted to change the nitrogen protection of **80**

from benzoyl to the *tert*-butoxycarbonyl group. This was accomplished by acyl group transfer of the benzoyl-protected diketopiperazine **80** with glycine methyl ester, providing **81** in 85% yield. Alternatively, phosphonate ester **82** could be olefinated in 75% yield

Scheme 19



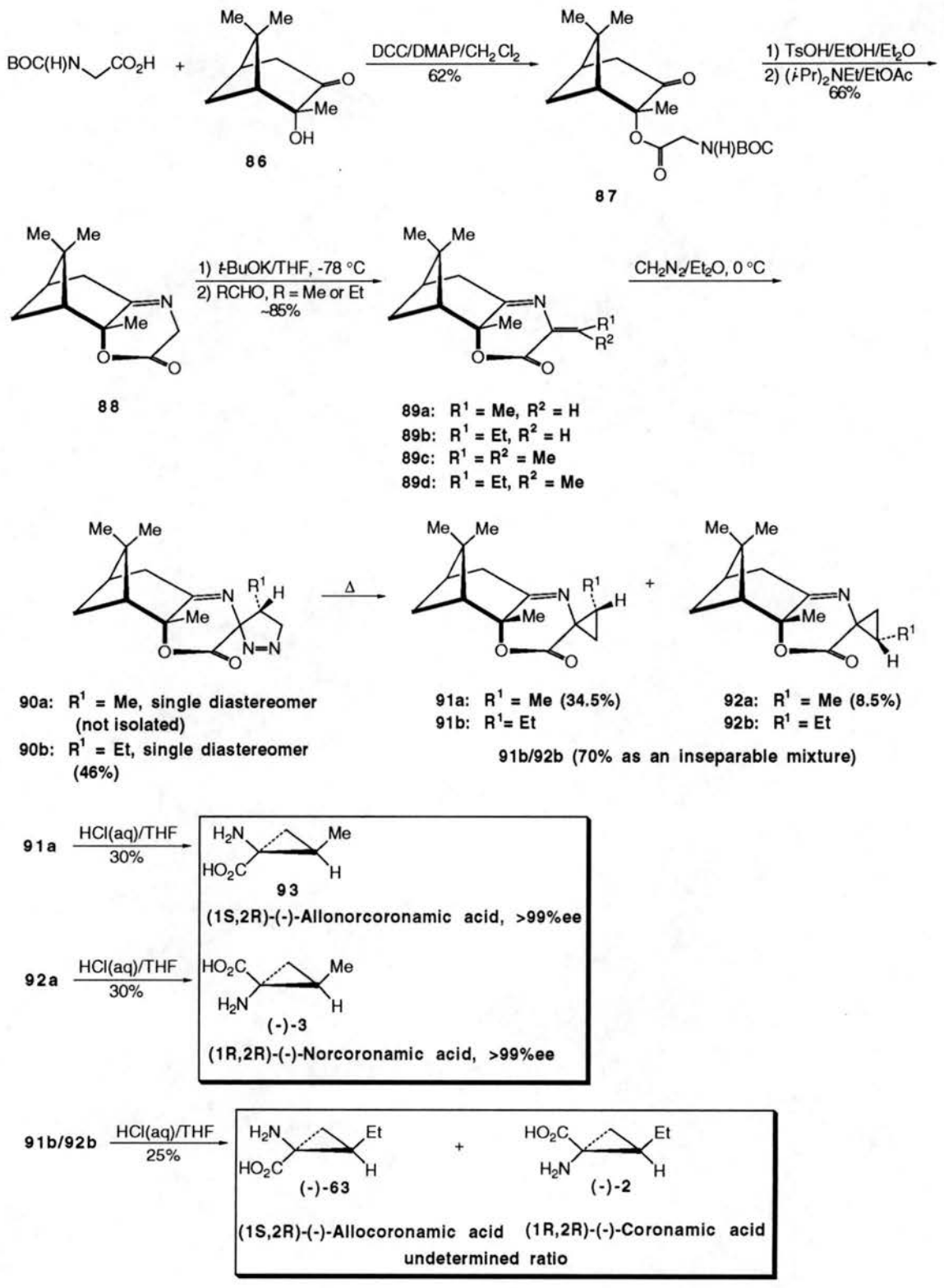
(Z/E ratio = 9:1) by the Emmons-Horner-Wadsworth procedure using propionaldehyde. Alkene **81** was protected with di-*tert*-butyldicarbonate to give **83** in 75% yield and then

cyclopropanated in the usual way,[15q] providing spirocyclopropane (**85**) in quantitative yield and 90% de. Acidic hydrolysis of **85** followed by ion-exchange chromatography afforded (1R,2S)-(+)-allocoronamic acid (**63**) in 66% yield and 90% ee. Again, the authors provide no explanation for the incredibly high stereoselectivity observed for the cyclopropanation reaction.

Viallefont and coworkers[15s] have recently described the asymmetric syntheses of both the (Z)- and (E)-isomers of MeACC and EtACC using (1R,2R,5R)-2-hydroxy-3-pinanone (**86**) as chiral auxiliary (Scheme 20). The synthesis began with the esterification of N-*t*-BOCglycine with commercially available (+)-2-hydroxy-3-pinanone (**86**)[37] to give ester **87** in 62% yield. Removal of the *t*-BOC functionality of **87** using *p*-toluenesulfonic acid preceeded spontaneous cyclization to imine **88** in 66% yield. Generation of the enolate of **88** followed by Aldol addition to acetaldehyde and propionaldehyde, gave exclusively the (Z)-alkenes **89a** and **89b** in 85% yield after dehydration of the initial aldol adducts. Treatment of **89a** with an ethereal solution of CH_2N_2 at 0 °C produced a single pyrazoline diastereomer **90a** as determined by ^{1}H NMR. Evaporative workup of the pyrazoline intermediate produced a mixture of 17% recovered **89a**, 30% (Z)-olefin **89c**, and the two cyclopropane derivatives **91a** and **92a**, in 34.5% and 8.5% yields, respectively. Assuming the ^{1}H NMR assignment of **90a** to be correct, the thermal decomposition mode of this pyrazoline causes considerable scrambling in the cyclopropane-forming reaction. Product **89c** is a result of nitrogen extrusion of **90a** in concert with a 1,2-hydride shift of the methine hydrogen atom. Acidic hydrolysis of both **91a** and **92a** afforded (1S,2R)-(-)-allocoronamic acid and (1R,2R)-(-)- norcoronamic acid in 30% yield as single diastereomers.

Diazomethane addition to **89b** produced pyrazoline **90b** in 46% yield, in addition to recovered **89b** (36%) and (Z)-alkene **89d** (18%). A solution of **90b** was heated in toluene for three hours, affording **89d** in 30% yield and an inseparable mixture of **91b** and **92b** in 70% yield. The ratio for **91b/92b** was not reported. Hydrolysis of this mixture with HCl(aq)/THF furnished a mixture of (1S,2R)-(-)-allocoronamic and (1R,2R)-(-)-coronamic acids (**63**) and (**2**) in only 25% yield. The authors incorrectly assigned a ratio to the mixture of amino acids based only on comparing optical rotation values with those previously reported. The same methodology can be applied towards the preparation of the enantiomeric series of MeACC and EtACC by replacing chiral auxiliary **86** with its enantiomer, (1S,2S,5S)-(-)-2-hydroxy-3-pinanone. Two troubling aspects of this methodology are the poor selectivities in the cyclopropanation reactions and the relatively

Scheme 20



86

87

88

89a: R^1 = Me, R^2 = H
89b: R^1 = Et, R^2 = H
89c: R^1 = R^2 = Me
89d: R^1 = Et, R^2 = Me

90a: R^1 = Me, single diastereomer (not isolated)
90b: R^1 = Et, single diastereomer (46%)

91a: R^1 = Me (34.5%)
91b: R^1 = Et

92a: R^1 = Me (8.5%)
92b: R^1 = Et

91b/92b (70% as an inseparable mixture)

91a → **93**
(1S,2R)-(-)-Allonorcoronamic acid, >99%ee

92a → **(-)-3**
(1R,2R)-(-)-Norcoronamic acid, >99%ee

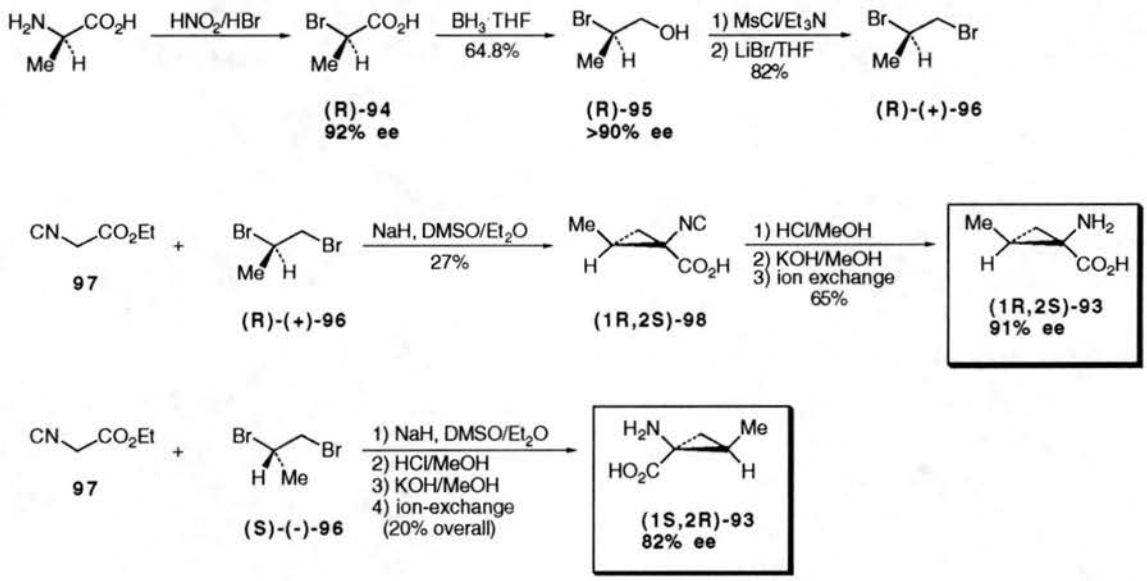
91b/92b → **(-)-63** + **(-)-2**
(1S,2R)-(-)-Allocoronamic acid (1R,2R)-(-)-Coronamic acid
undetermined ratio

poor yields observed during removal of the chiral auxiliary. Hopefully the authors will investigate the use of other cyclopropanating reagents and further refine the hydrolytic deprotection step and subsequent recovery of the auxiliary **86**.

1.4 Stereocontrolled Syntheses of 1-Aminocyclopropane-1-carboxylic Acids

Pirrung and McGeehan[14g] synthesized (1R,2S)- and (1S,2R)-2-methyl-1-aminocyclopropane-1-carboxylic acids from the chiral synthons (R)-(+)- and (S)-(-)-1,2-dibromopropanes (**96**) (Scheme 21). The synthesis began with the preparation of the

Scheme 21



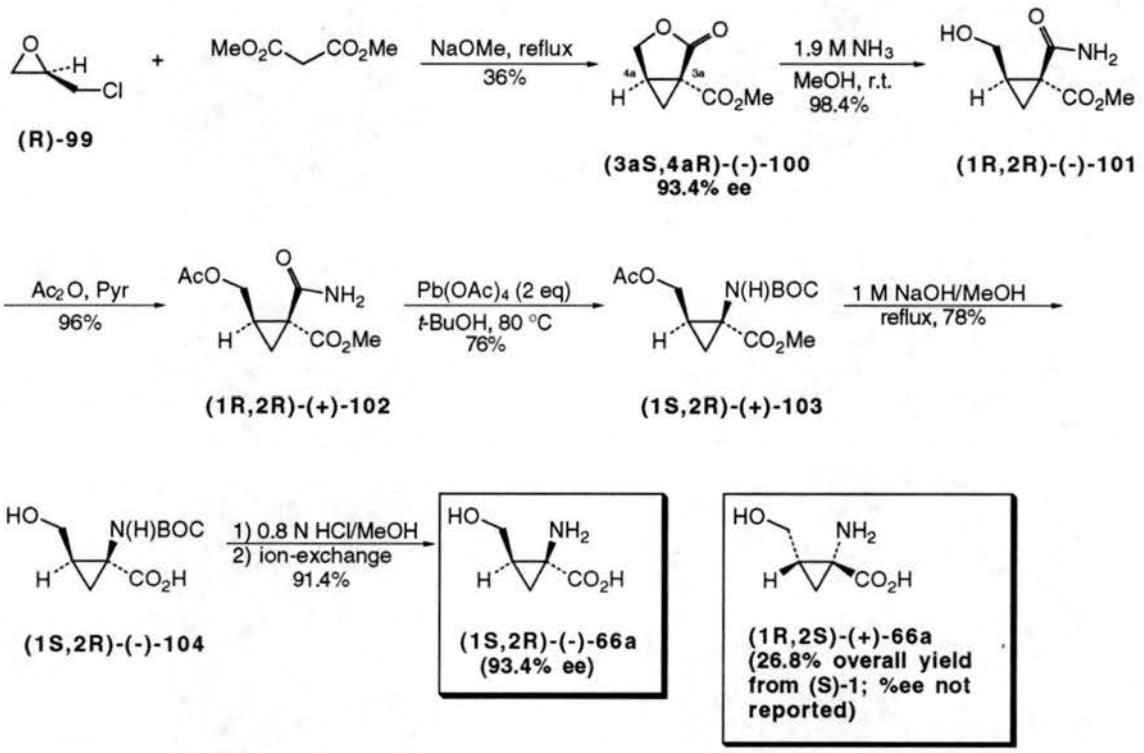
enantiomerically enriched 1,2-dibromopropanes (**96**) from either (D)- or (L)-alanine, respectively. According to the procedure of Amarego and associates,[38] (D)-alanine was diazotized and subsequently brominated to give (R)-2-bromopropionic acid (**94**) (yield not reported) in 92% ee. Reduction of **94** using BH_3·THF complex gave bromoalcohol **95** in 65% yield and greater than 90% ee based on ^{19}F NMR analysis of the MTPA ester.[39] Alcohol **95** was then converted into (R)-(+)-1,2-dibromopropane (**96**) using standard mesylation and bromination conditions in 82% yield. In similar fashion, (S)-(-)-**96** was manufactured from (L)-alanine.

The synthesis of the MeACC enantiomers was achieved by applying the cycloalkylation procedure of Schöllkopf[14a] in which ethyl isocyanoacetate (**97**) functions as a protected glycine dianion. Thus, treatment of a mixture of **97** and (R)-(+)-1,2-

dibromopropane (**96**) with NaH in DMSO/ether afforded (1R,2S)-ethyl 2-methyl-1-isocyanocyclopropane-1-carboxylate (**98**) in 27% distilled yield. A standard two step hydrolysis of **98** furnished (1R,2S)-(+)-2-methyl-1-aminocyclopropane-1-carboxylic acid (**93**) in 65% yield and 91% ee (determined by ^{19}F NMR of the corresponding MTPA amide derivative[39]). The antipode of **93** was prepared in 20% overall yield and 82% ee by applying the same three step procedure with (S)-(-)-**96** serving as the dielectrophile.

Pirrung and coworkers[141] reported highly diastereoselective syntheses of (1S,2R)- and (1R,2S)-1-amino-2-(hydroxymethyl)cyclopropane-1-carboxylic acids (**66a**), initiated again by the cycloalkylation ploy of dimethyl malonate shown in Scheme 22. The

Scheme 22

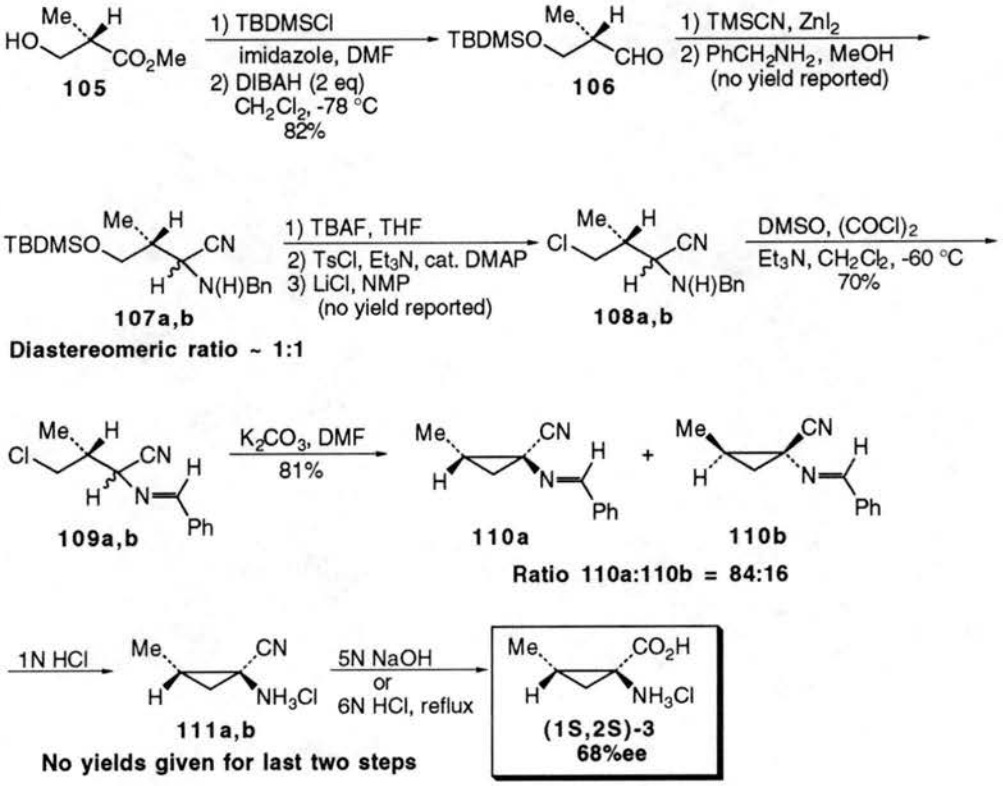


synthesis of (1S,2R)-**66a** began by treating dimethyl malonate with NaOMe followed by (R)-epichlorohydrin (**99**)[40] to furnish (3aS,4aR)-(-)-lactone **100** in 36% yield and 93.4% de. The diastereomeric excess was determined by ^{19}F NMR analysis of the Mosher ester of **104** (later in the synthesis) and the absolute configurational assignment made from comparison of the optical rotation of (-)-**100** to that of lactonized cyclopropane-1,1-dicarboxylates of known absolute configuration.[41] Regioselective ammonolysis and acetylation of (-)-**100** provided amide **102** in 94% yield. Hoffmann rearrangement of **102** was accomplished by lead tetraacetate in *t*-BuOH to give the triprotected amino acid **103** in

76% yield. Standard deprotection of **103** in two steps afforded (1S,2R)-(-)-**66a** in 71.3% yield and 93.4% de. The synthesis of (1R,2S)-(+)-**66a** was achieved in similar fashion by substituting (R)-**99** with (S)-**99**[42] in the first reaction of the sequence.

Salaün and coworkers[43] have prepared (1S,2S)-norcoronamic acid (**3**) from the commercially available (S)-(+)-methyl 3-hydroxy-2-methyl propionate (**105**) as shown in Scheme 23. Propionate **105** was first silylated with *tert*-butyldimethylsilyl chloride and

Scheme 23



then reduced by DIBAH to give (S)-aldehyde (**106**) in 82% yield. Addition of trimethylsilyl cyanide at 0 °C to **106** in the presence of catalytic zinc iodide provided the corresponding α-trimethylsilyloxynitrile, which undergoes subsequent amination by benzylamine, thus affording a 55:45 diastereomeric mixture of α-aminonitriles **107a** and **107b**. Removal of the silyl protecting group with TBAF, followed by chemoselective O-tosylation (TsCl, Et_3N, cat. DMAP) and conversion of the resulting O-tosylate with LiCl in N-methylpyrrolidone gave diastereomeric chlorides **108a,b**. Swern N-oxidation[44] of **108a,b** using the traditional Swern conditions produced chloroimines **109a,b** in 70% yield. Cyclization of these intermediates was achieved after treatment with K_2CO_3 in DMF, to furnish cyclopropanes **110a** and **110b** in 81% yield and a ratio of 84:16, respectively. Finally, a two step hydrolysis of **110a,b** gave (1S,2S)-norcoronamic acid

(**3**) in 68% de. Further diastereoenrichment of **3** was achieved via the enzymatic resolution technique employed by Baldwin and associates.[45]

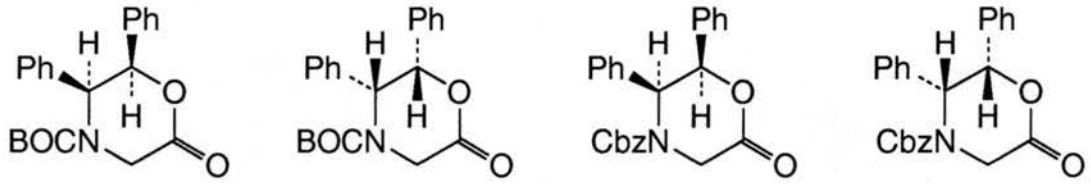
Chapter 2

Results and Discussion

2.1 Asymmetric Syntheses of (1S,2S)-2-Alkyl-1-Aminocyclopropane-1-carboxylic Acids

During the past decade the Williams' research group has actively engaged in the asymmetric syntheses of numerous natural and unnatural α-amino acids.[46] Essentially all of this work is based on carbon-carbon bond-forming reactions about the α-carbon of the commercially available,[47] chiral non-racemic lactones **112** and **113** (Figure 4). These

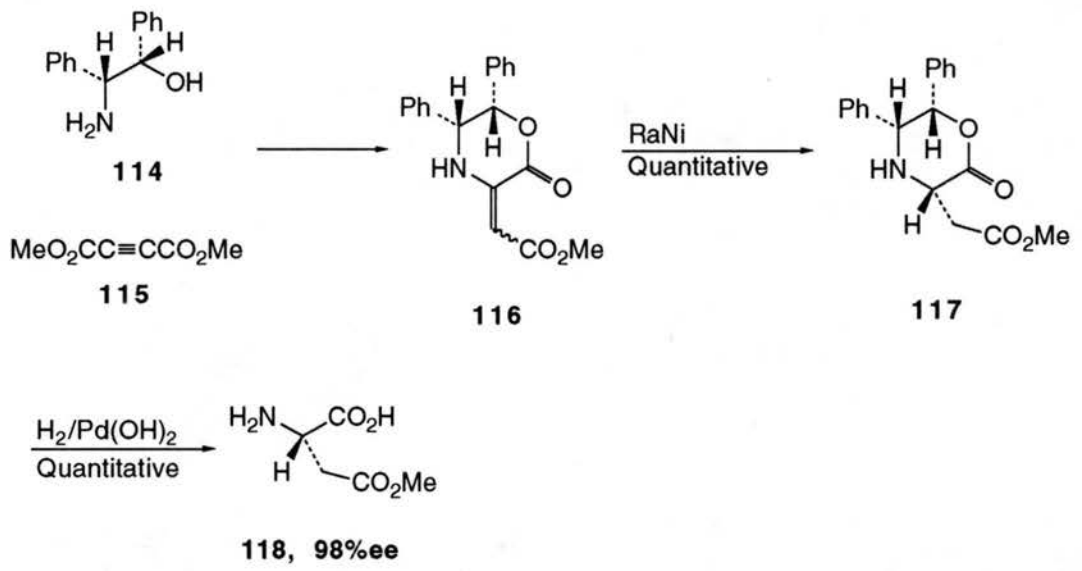
Figure 4



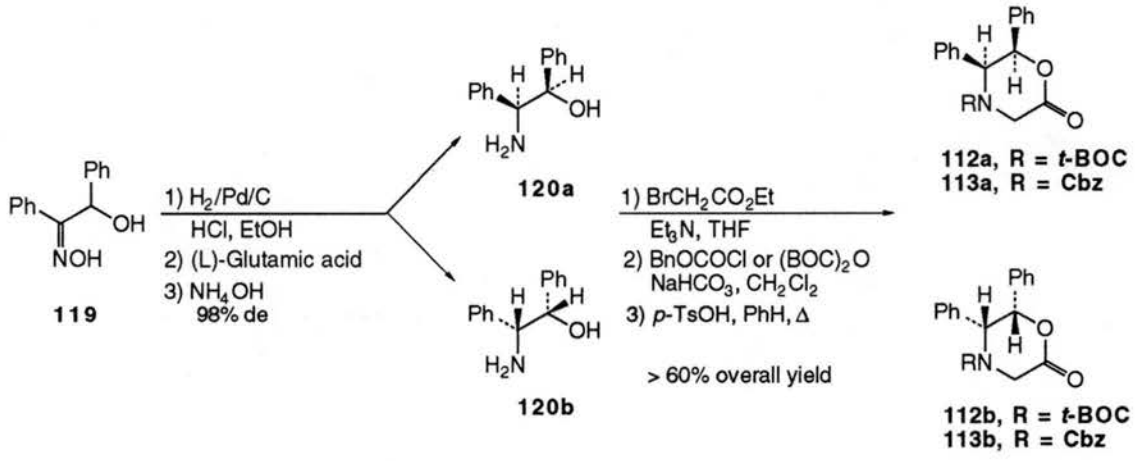
optically pure glycinate auxiliaries were designed and prepared based on the successful synthesis of a similar heterocycle reported by Horeau and coworkers.[48] In this work (Scheme 24), erythro-1,2-diphenylethanolamine (**114**)[49] was condensed with dimethyl acetylenedicarboxylate (**115**) to afford the α,β-unsaturated lactone derivative **116**. Reduction of the carbon-carbon double bond of **116** with Raney nickel provided **117** in quantitative yield. Hydrogenolytic removal of the auxiliary was accomplished using two atmospheres of hydrogen gas and palladium (II) hydroxide as catalyst, thus generating β-methyl aspartate (**118**) in quantitative yield and in 98% ee. The attractive feature of this synthesis is the relative ease of unmasking intermediate **117** to the free amino acid.

Preparation of the optically pure glycinates **112** and **113** is accomplished via a simple six step procedure shown in Scheme 25. Commercially available α-benzoin oxime (**119**) is stereospecifically hydrogenated to racemic erythro-amino alcohols (**120**) which are subsequently resolved as the L-glutamate salts[49a] on large scale. Amino alcohols **120a** and **120b** are each obtained in greater than 98% ee as stable crystalline solids.[50] Each enantiomer is then individually alkylated with ethyl bromoacetate, acylated with either di-*tert*-butyl dicarbonate or benzylchloroformate, and finally lactonized by treatment with catalytic *para*-toluenesulfonic acid in refluxing benzene (while azeotroping H_2O) to afford lactones **112/113** in greater than 60% overall yield from amino alcohols **120a/b**. Remarkably, the entire process requires absolutely no chromatographic separations and the lactones **112/113** are stable crystalline solids with essentially indefinite shelf-life storage properties.

Scheme 24

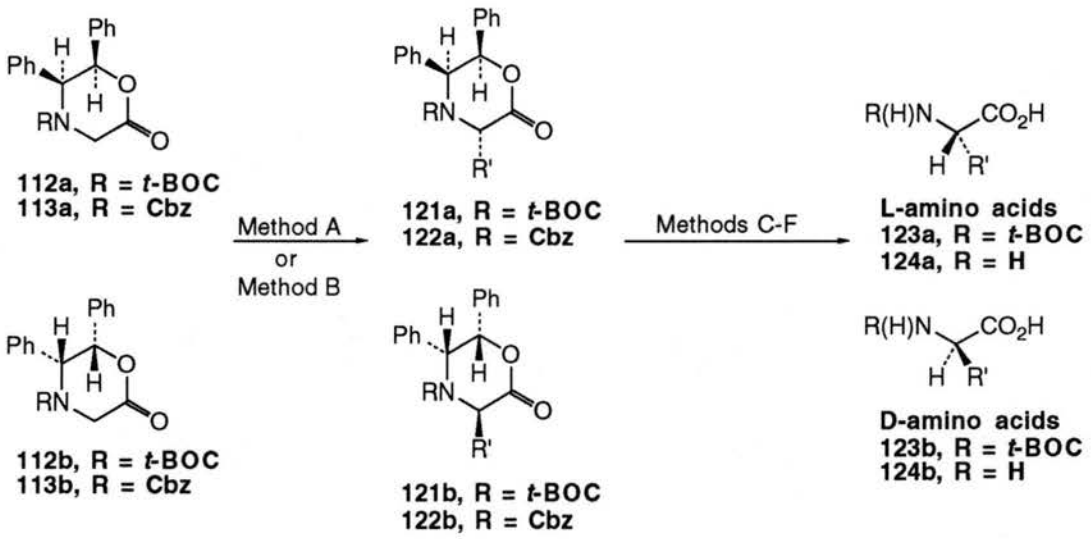


Scheme 25



One significant advantage to these chiral auxiliaries comes from the fact that they allow access to the synthesis of L- or D-configured amino acids after derivatization (methods A or B) of the α-carbon (Scheme 26). Thus, lactones **112a/113a** generally lead to L(or S)-amino acids while lactones **112b/113b** provide D(or R)-amino acids. Another key advantage in using lactones **112/113** as chiral templates stems from the relative ease of unmasking (methods C-F) the auxiliary unit from the alkylated derivatives **121/122** to afford the corresponding amino acids **123/124** in typically high yields and high optical purity. Deprotection method C is generally used for lactones **121a/b** where R' represents an unsaturated appendage or when *t*-BOC-protected amino acids **123a/b** are desired for

Scheme 26



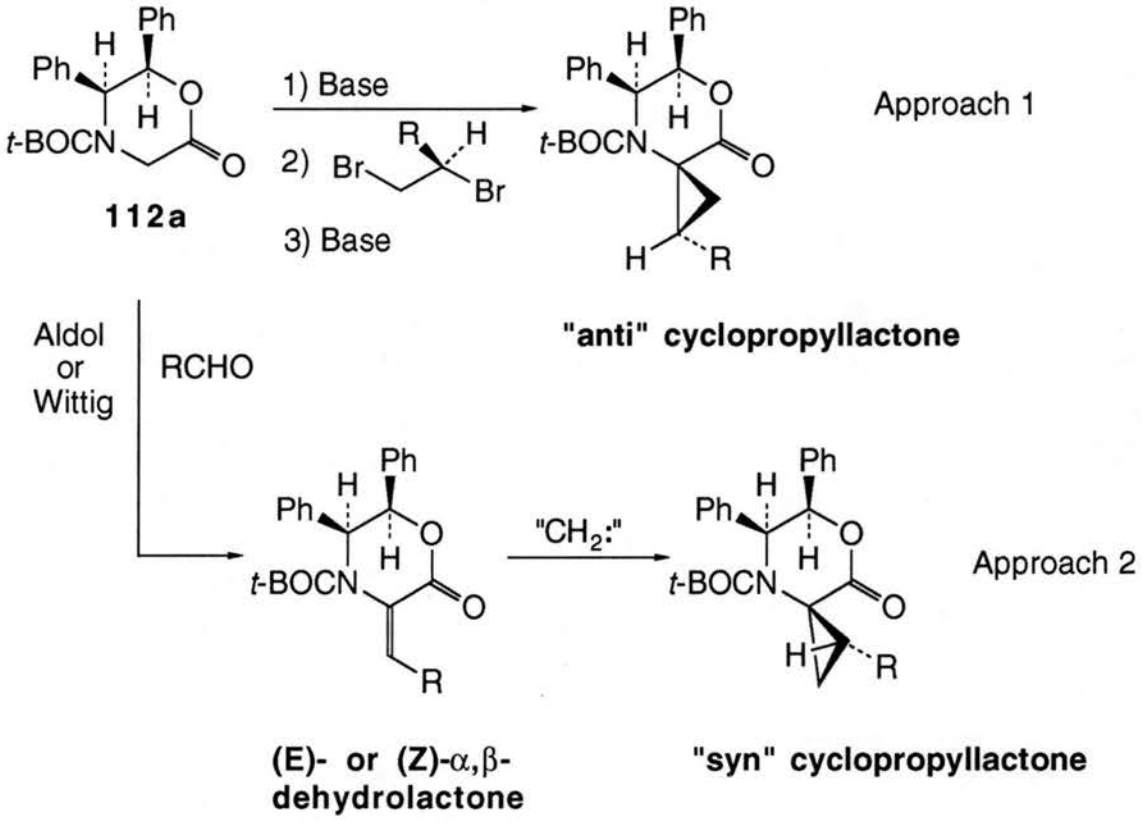
Method A: 1) NBS, CCl_4, reflux; 2) R'M(M = metal), $ZnCl_2$, THF
Method B: 1) $LiN(SiMe_3)_2$, R'X
Method C: 1) Li°/NH_3, EtOH, THF, -78 °C; 2) NH_4Cl
Method D: cat. $PdCl_2$, 20-50 psi H_2(g)
Method E: 1) Me_3SiI, CH_2Cl_2; 2) 10% HCl/THF reflux; 3) $NaIO_4$ H_2O, THF, pH = 3
Method F: 1) TFA, CH_2Cl_2; 2) LiOH(aq)/EtOH; 3) CH_2N_2; 4) $Pb(OAc)_4$, MeOH/CH_2Cl_2, -15 °C; 5) HCl (aq)/THF; 6) $(BOC)_2O$, Et_3N, THF

further manipulation. If one wishes to obtain the pure free amino acids **124a/b**, deprotection method D applied to lactones **122a/b** is preferred. Method E is suitable for the deprotection of lactones **121a/b** in which R' is an aromatic group and where base-induced epimerization of the α-carbon is a major concern. Finally, the most recent method developed for chiral auxiliary removal, method F, is used in special cases where based-induced epimerization at the α-center of **121a/b** is problematic or where strongly acidic conditions cause decomposition of the desired amino acid species.

In devising a strategy for the synthesis of 1-aminocyclopropane-1-carboxylic acid derivatives from lactones **112/113**, two methods were considered as viable options (Scheme 27). The first consideration, Approach 1, would involve tandem dialkylation of **112a/112b**[51] with a 1,2-dibromoalkane or a similar dielectrophile to afford the predicted "anti" cyclopropyllactones in potentially high diastereomeric excess. Previous work in the Williams' laboratories involving the dialkylation of **112** or **113** to form α-disubstituted α-amino acids has shown that excellent selectivities (> 99% ee) can be achieved.[46j,k] Unfortunately, precedented asymmetric versions[14h,i,j,l] of the tandem

dialkylation (cycloalkylation) approach (eqs 1 and 2, Figure 3, Chapter 1) generally proceed with only poor to moderate stereoselectivity (Schemes 9, 12, 14, 15, Chapter 1). Therefore, a more reliable approach was sought as a starting point.

Scheme 27

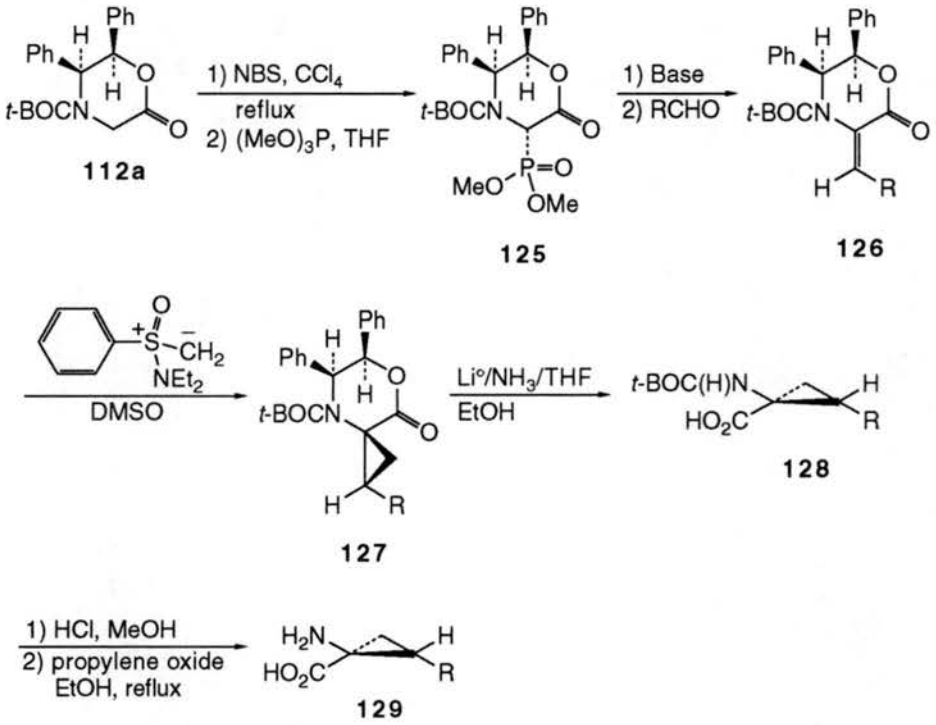


It seemed reasonable to expect that lactones **112a/112b** could be converted to (E)- or (Z)-α,β-dehydrolactones which could in turn be stereoselectively cyclopropanated to afford the predicted "syn" cyclopropyllactone, assuming that the olefin geometry could be controlled and that delivery of the methylene unit of the cyclopropanating agent would occur preferentially and predictably from the least hindered face of the carbon-carbon double bond (Scheme 27, Approach 2). Based on earlier reports[15o,r] of asymmetric cyclopropanations of dehydroamino acid derivatives (see eq 3, Figure 3; and Schemes 17 and 19, Chapter 1), this second synthetic approach appeared to hold more promise than that of the tandem alkylation ploy.

Preliminary attempts to synthesize E- or Z-α,β-dehydrolactones via straightforward aldol condensations failed miserably. Deprotonation of oxazinone **112a** in the standard fashion,[46j,k] followed by treatment with excess acetaldehyde gave complex mixtures of products; presumably acetaldehyde rapidly self-condensed rather

than react in the desired mode. Immediately, attention was turned to the conversion of **112a** into a Wittig-type reagent which could react with various aldehydes and thus give the desired α,β-dehydrolactone derivatives. Such Wittig precursors could be accessed from the α-bromolactone (Step1, Method A, Scheme 26) via displacement of bromide by triphenylphosphine to give a phosphonium ion or by an Arbuzov displacement with a trialkylphosphite to afford the corresponding α-dialkylphosphoryllactone.[52] The latter of these two options prevailed. Lactone **112a** was readily brominated as previously detailed[46a-f] with 1.1 molar equivalents of N-bromosuccinimide (NBS) in refluxing CCl_4[53] to afford, after cooling and filtration of insoluble succinimide, the α-bromolactone as an amorphous white solid (Scheme 28).

Scheme 28



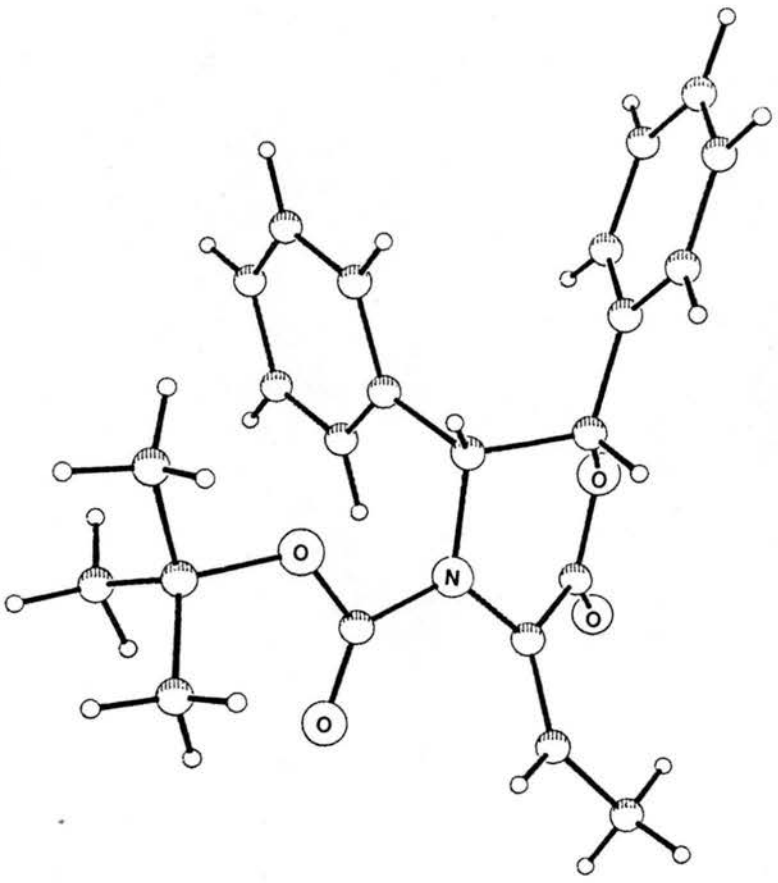
The crude bromide was immediately dissolved in THF and gently refluxed with a slight excess of trimethylphosphite to provide the white crystalline phosphonate ester **125** in 86% overall yield. The stereochemistry of **125**, although depicted in Scheme 28 as *anti* between the phosphoryl and phenyl groups, has not been assigned and is of no consequence in the subsequent Horner-Emmons-Wadsworth olefination r eactions. Thus treatment of **125** with base and an aldehyde[54] provided the (E)-α,β-dehydrolactone adducts **126** in generally high yields (Table 1). The assignment of the E stereochemistry was firmly established for **126b** and **126f** by x-ray crystallographic analysis (Figures 5

and 6, respectively). Since all of the final amino acids have a *cis* orientation of the carboxyl and R groups (vida infra), it follows that **126c-e** and **126g-i** also possess the E stereochemistry.

Table 1. Preparation of α,β-Dehydrolactones **126**.

entry	aldehyde	rxn conditions	% yield **126**	H = ; R =
1	^2H_2CO	NaH/THF	**126a**, 100	^2H, ^2H
2	MeCHO	LDA/THF	**126b**, 93	H, Me
3	EtCHO	LDA/THF	**126c**, 92	H, Et
4	PrCHO	LDA/THF	**126d**, 82	H, *n*-Pr
5	*i*-PrCHO	LDA/THF	**126e**, 19	H, *i*-Pr
6	PhCHO	NaH/benzene	**126f**, 96	H, Ph
7	*p*-NO_2PhCHO	NaH/benzene	**126g**, 84	H, *p*-NO_2Ph
8	*p*-MeOPhCHO	NaH/benzene	**126h**, 84	H, *p*-MeOPh
9	3,5-$(MeO)_2$PhCHO	NaH/benzene	**126i**, 62	H, 3,5-$(MeO)_2$Ph

Figure 5. X-ray stereostructure of **126b**. Spheres are of fixed arbitrary radii.



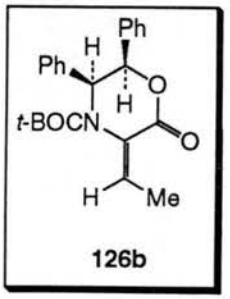
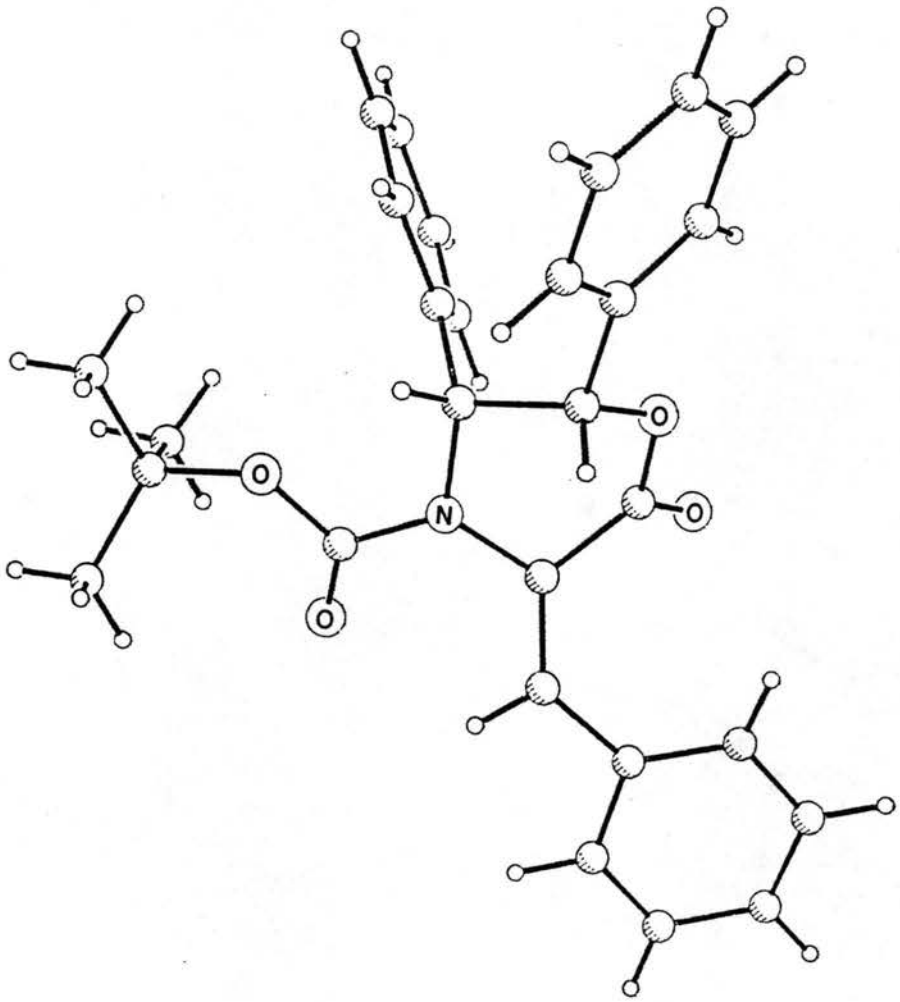
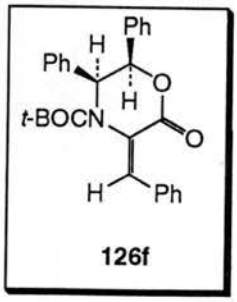


Figure 6. X-ray stereostructure of **126f**. Spheres are of fixed arbitrary radii.



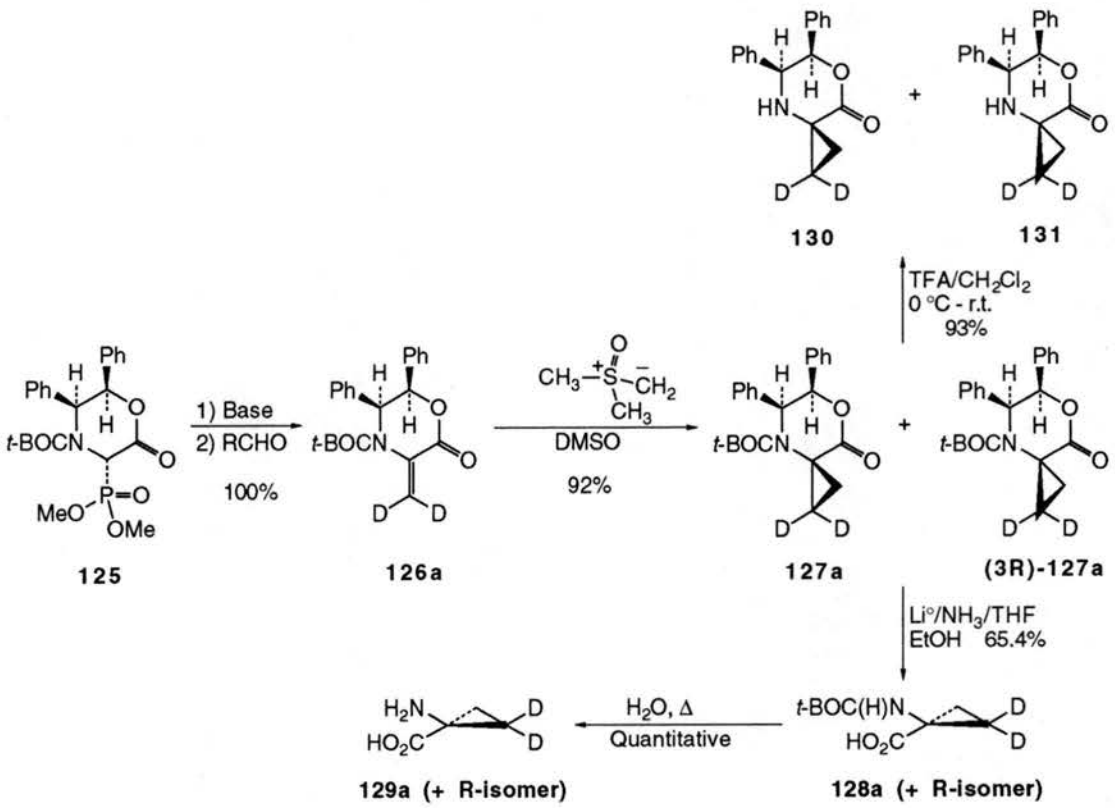


126f

One further comment should be made about the Emmons-Horner-Wadsworth olefination process. Enolizable aliphatic aldehydes (entries 2-5, Table 1) were condensed with the LDA-generated phosphonate ester anion between -15 °C and room temperature. These conditions proved unsatisfactory for olefinations involving aromatic aldehydes (entries 6-9, Table 1). This problem was solved by refluxing aromatic aldehydes with a slurry containing NaH, phosphonate ester **125**, and benzene while slowly distilling away solvent into a Dean-Stark trap. In this way, E-α,β-dehydrolactones **126f-i** were obtained in good to excellent yields.

Attention was then directed to finding a reagent which could cyclopropanate **126** in a highly stereoselective fashion. The first such reagent attempted in this endeavor was the Corey ylide, dimethyloxosulfonium methylide.[55] Upon treatment of **126a** with one molar equivalent of the NaH-derived ylide, cyclopropanation products were obtained in 92% yield(Scheme 29). Initially, the reaction appeared to be 100% stereoselective as

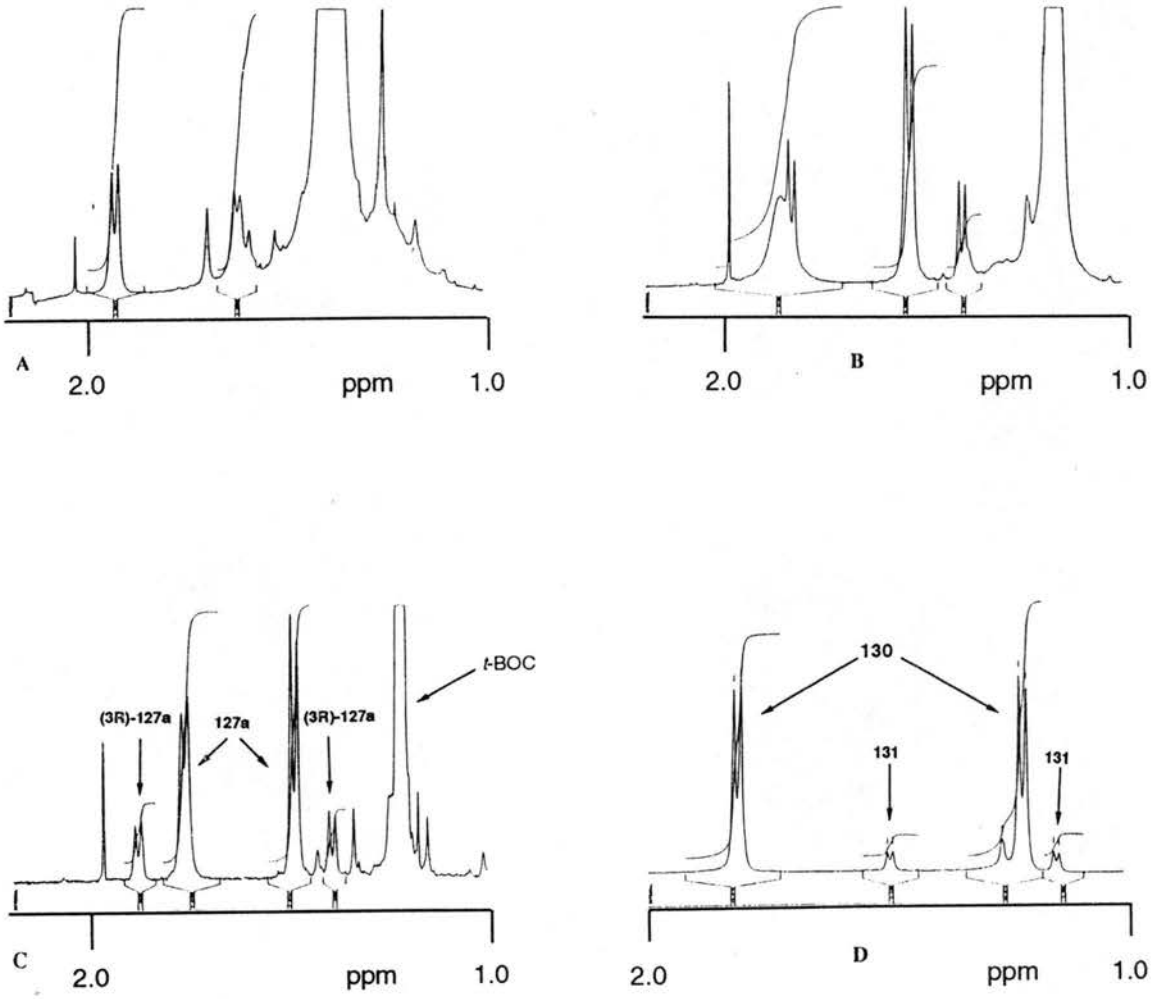
Scheme 29



determined by ^1H NMR[56] in $CDCl_3$ (Figure 7, Spectrum A). However, when the product was analyzed in DMSO-d_6 (Figure 7, Spectrum B) the pair of doublets representing the diastereotopic cyclopropyl methylene protons split into a partially

resolved four doublet system, representing not one, but rather two diastereomers in approximately a 3:1 ratio (**127a** : **(3R)-127a**). High temperature (ca. 75-100 °C) ^{1}H NMR provided an unambiguous time-resolved spectrum (Figure 7, Spectrum C) clearly showing a major and minor diastereomer. Also, the ^{1}H NMR spectra of **127a/(3R)-127a** were only useful for a crude estimation of the diastereomeric ratio since baseline resolution of the *tert*-butoxycarbonyl and cyclopropyl resonances could not be accomplished. In order to obtain a more accurate ratio, **127a/(3R)-127a** were deblocked with 20 equivalents of TFA in CH_2Cl_2 between 0 °C and room temperature to provide **130/131** in 93% yield.

Figure 7. Cyclopropyl resonances from ^{1}H NMR spectra of **127a/(3R)-127a** in $CDCl_3$ (A); DMSO-d_6 at 297 K (B); DMSO-d_6 at 325 K (C); and **130/131** in $CDCl_3$ (D). Spectra A-C were derived from **126a** and dimethyloxosulfonium methylide; D was derived from **126a** and [(diethylamino)phenyl]oxosulfonium methylide.



Removal of the *t*-BOC moiety was used subsequent to all cyclopropanations of **126a** and the ^{1}H NMR of **130/131** was used exclusively to determine the diastereomeric excess and thus, the enantiomeric excess of the final amino acid.[57] The facial selectivity of this reaction (vide infra) was not in accord with the prediction that attack of the cyclopropanating reagent should occur from the less hindered face of the lactone, *anti* to the two phenyl rings. The fundamental basis for this stereoselectivity is at present, undetermined. Confirmation that the stereoselectivity of this cyclopropanation gave **127a** as the major isomer was obtained by conversion of the derived amino acid **129a** (as a mixture with the inseparable R-isomer) into the corresponding L-phenylalanine diketopiperazine (**30**) (see Scheme 8 Chapter One) and comparison of the chemical shifts for the cyclopropyl methylene protons with those reported by Arigoni and associates on the same substance.[12b]

It is not clear whether the disappointing diastereoselectivity of the Corey ylide is a consequence of poor facial discrimination of the ylide on the α- and β-faces of the olefin or a result of β,γ-rotation of the enolate adduct prior to displacement of DMSO or a combination of both effects. Nonetheless, these results prompted an investigation of alternative cyclopropanating reagents. It seemed reasonable that a 1,3-dipolar cycloaddition of diazomethane to **126a** would produce the desired diastereofacial selectivity [15o,r] and should also preclude the possibility of bond rotation prior to formation of a spirocyclic adduct (in the present case, a pyrazoline). In spite of the unexpected facial preference for the Corey ylide discussed above, it was expected that attack of the 1,3-dipole should occur from the less hindered α-face due to steric interference from the C-5 and/or C-6 phenyl rings. In the event, when **126a** was treated with 10 mol equiv of CH_2N_2 in Et_2O/THF a mixture of pyrazolines (which were stable to silica gel chromatography) was produced. Subsequent photolysis of the mixture in a quartz tube, gave **127a** and **(3R)-127a** in a diastereomeric ratio of 1 : 2~3. This sense of facial selectivity is opposite to that obtained from the dimethyloxosulfonium methylide reaction and was in accord with the expectation that the α-face of the α,β-dehydrolactone should be more accessible. The relatively poor diastereoselection was disappointing and prompted a more detailed examination of additions to the double bond.

Closer analysis of the steric environment about the α- and β-face of the dehydrolactone systems (Figure 9) was made possible through x-ray crystallography. Contrary to expectation, examination of the x-ray crystal structures of **126b**, **126f**, and **126a** (Figures 5,6, and 10, respectively) does not reveal convincing evidence that the C-5 phenyl ring significantly blocks the β-face of the olefin. As can be observed in Figure 10 for **126a**, the C-5 phenyl group is situated in a *quasiaxial* disposition relative to the

Figure 9

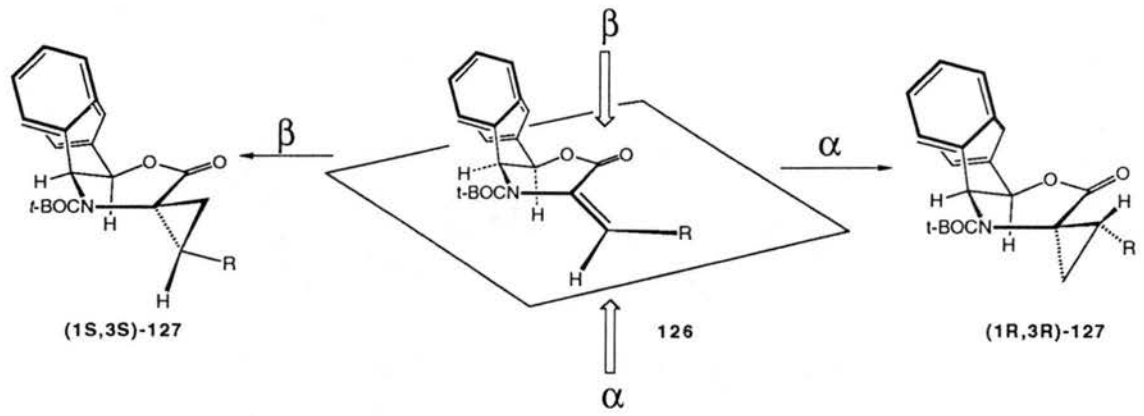
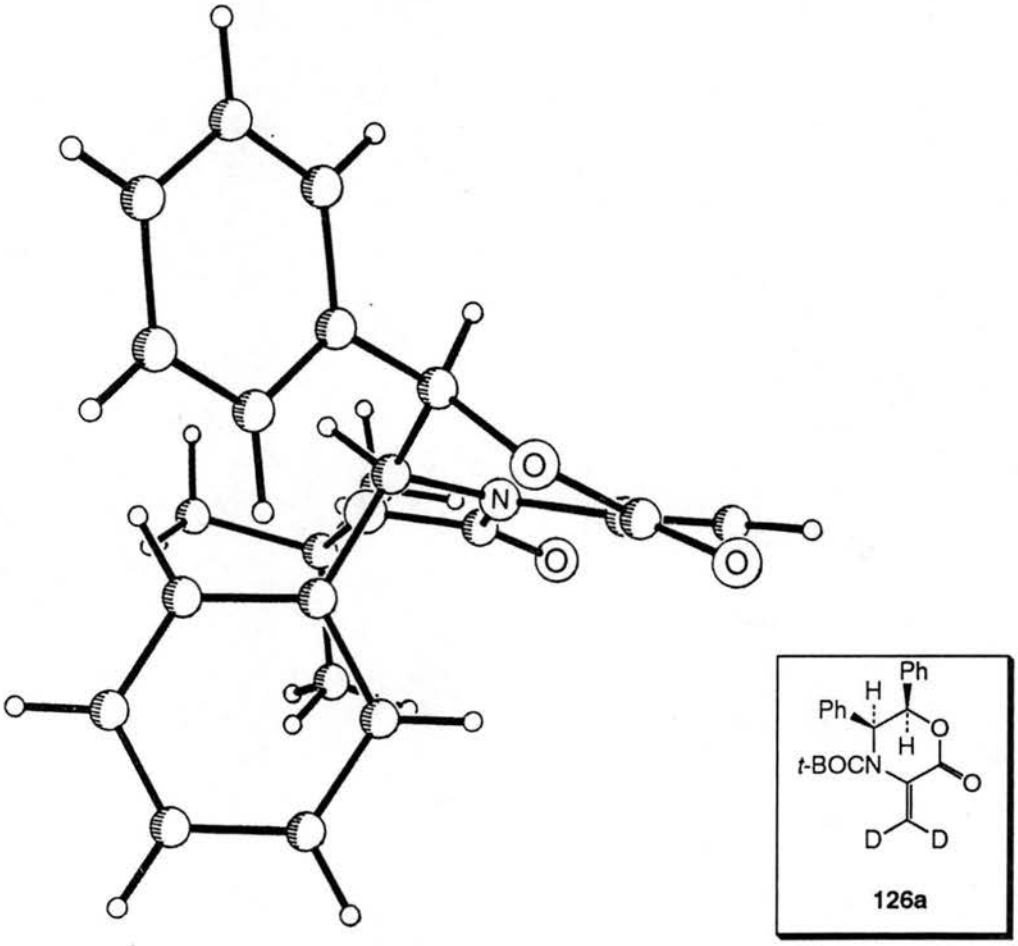


Figure 10. X-ray stereostructure of **126a**. Spheres are of fixed, arbitrary radii.



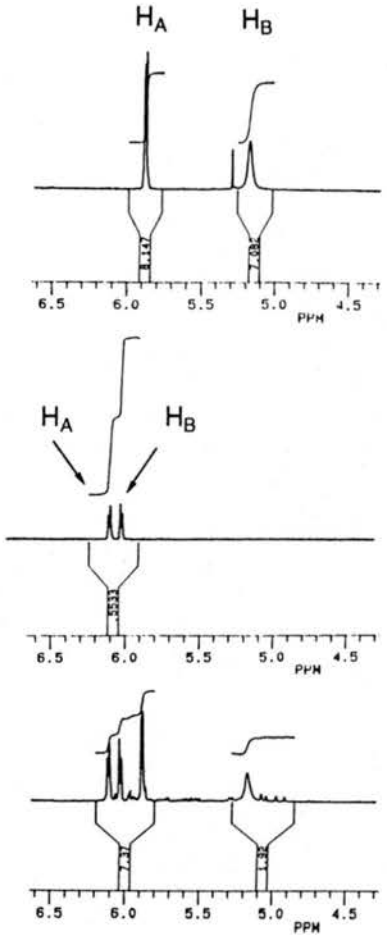
boat-shaped lactone ring. However, unlike the reactive intermediates of these lactone systems with an *endo* π-system (ie., enolate or iminium of **112a** [1a-f,j,k,l] ; see also the x-ray of the *trans*-allyl lactone template previously recorded from this laboratory [1b]) the olefinic geometry of **126** (*exo* π-system) appears to orient the lactone α-carbon further away from the sphere of the C-5 phenyl ring (see Figures 5,6, and 10) and may account for the poorer facial discrimination relative to the iminium or enolate ions derived from **112a**. A manifestation of this situation is the lack of co-planarity of the lactone carbonyl and the α,β-double bond. The dihedral angle between the α,β-alkenyl system and lactone carbonyl for **126a**,**126b** and **126f** ranges from 22°-43° illustrating significant lack of conjugation between the respective π-systems.

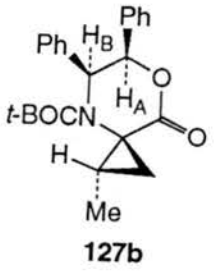
In similar fashion, when compound **126b** was treated with diazomethane followed by photolysis of the pyrazoline intermediate, a separable mixture (91%) of diastereomeric cyclopropanes (**127b** + 1R,3R-diastereomer) in a ratio of 1:1.6 was obtained. As shown in Figure 11, the partial ^{1}H NMR spectra for both diastereomers are displayed along with that of the crude mixture. The benzylic methine protons at C-5 and C-6, serve as a useful handle for assessing the diastereomeric ratio. It was later observed that the pyrazoline diastereomers obtained from **126b** were also separable by flash chromatography in the dark and could be cleanly and stereospecifically photolyzed to **127b** plus the corresponding 1R,3R-diastereomer as a toluene solution in quartz glass.

To test the limits of diazoalkane additions to adducts **126**, a solution of diphenyldiazomethane in EtOAc [58] was added to unlabelled **126a** and stirred for 11 days. The corresponding diphenylcyclopropane was obtained in 93% yield as a 6.2:1 mixture of diastereomers (relative stereochemistry not assigned). With this disappointing level of diastereofacial induction, it was clear that the cycloaddtion approach would not provide the desired selectivity, regardless of whether bulky substituents were placed on the olefin or on the 1,3-dipole.

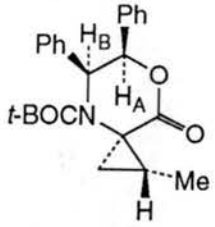
The third and final class of cyclopropanating reagents examined were (dimethylamino)- and (diethylamino)phenyloxosulfonium methylides , first prepared by Johnson and coworkers.[59] The chemistry of these ylides parallels that of dimethyloxosulfonium methylide with the added advantage of increased steric bulk and chirality on sulfur. It has been reported that the reaction between these ylides in their optically pure form and α,β-unsaturated carbonyl compounds proceeds to produce cyclopropanes with enantiomeric excesses up to 43.2%.[59b,d,f] Although these reagents have been known for over two decades,[60] no reports have appeared in which ACC derivatives were synthesized using these methylides. The preparation of the requisite ylides involves a straightforward, high yield, three step synthesis starting from

Figure 11. Benzylic methine resonances from ^1H NMR spectra for **127b** and the corresponding 1R,3R-diastereomer obtained from diazomethane addition to **126b**.





127b



(1R,3R)-127b

Mixture of **127b** and **(1R,3R)-127b**
Ratio = 1.0:1.6

thioanisole.[59c,d] Most significantly, these reagents gave greatly improved diastereoselectivities over those discussed above and gave the *same* sense of diastereofacial selection as that obtained with dimethyloxosulfonium methylide.

Cyclopropanation of **126a** with 2 molar equivalents of racemic (dimethylamino)phenyloxosulfonium methylide in DMSO at room temperature provided a 76% yield of **127a/(3R)-127a** (Scheme 29) in an approximate ratio of 6.3:1. Similar treatment of **126a** with (diethylamino)phenyloxosulfonium methylide provided cyclopropanes **127a** and **(3R)-127a** in 94.4% (as a 9.6:1 ratio). As expected, changing the amino alkyl substituent from methyl to ethyl on the ylide had a significant, albeit small, effect on the stereoselectivity of the cyclopropanation reaction. In addition, it was observed that by simply running the latter reaction at approximately 18 °C (freezing point of DMSO) followed by slow thawing, the ratio could be increased to 11:1. Utilizing the

same freeze-thaw technique, adducts **126b-f,h,i** gave excellent yields of the corresponding cyclopropanes and, furthermore only a single diastereomer (except for entry 11) was isolated in each case (Table 2). As mentioned previously, assignment of the diastereochemical ratios could be determined by quantitative analysis (e.g. integration) of the C-5 and C-6 benzylic methine protons by ^{1}H NMR .

With high levels of diastereoselectivity now accessible, it was necessary to deblock the cyclopropyl lactones to the free amino acids and thus rigorously determine the absolute stereochemistry of each. Thus, treatment of cyclopropanes **127a-d**

Table 2. Preparation of **127** via cyclopropanations of **126**.

entry	substrate	"CH_2:" reagent	**127**, % yield	diast. ratio[d]
1	**126a**	$Me_2SO(Me)I$[a]	**127a**, 98	2-3:1
2	**126b**	$Me_2SO(Me)I$[a]	**127b**, 77	2-3:1
3	**126a**	CH_2N_2[b]	**127a**, 100	1:2-3
4	**126b**	CH_2N_2[b]	**127b**, 91	1:1.6
5	**126a**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127a**, 97	11:1
6	**126b**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127b**, 82	1:0
7	**126c**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127c**, 79	1:0
8	**126d**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127d**, 88	1:0
9	**126f**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127f**, 96	1:0
10	**126h**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127h**, 68	1:0
11	**126i**	$Ph(Et_2N)SO(Me)BF_4$[c]	**127i**, 47	9.9:1

Reaction conditions: [a]NaH/DMSO, rt. [b]Diazomethane prepared from 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) and 5N NaOH (aq) at -15 °C. [c]NaH/DMSO, 18 °C→rt. [d]Ratios determined by ^{1}H NMR analysis.

with Li° in liquid NH_3 (Schemes 28 and 29) provided the N-*t*-BOC-protected amino acids (**128a-d**) in good yield (Table 3).

The arylcyclopropyllactone systems **127f-i** could obviously not be deprotected by dissolving metal reduction to the corresponding amino acids **128f-i** due to both the lability of the aromatic ring to reduction and the highly reactive benzylic cyclopropane bond; this was verified experimentally. The deprotection protocol employed for these systems will be discussed in Section 2.2.

To remove the *t*-BOC protecting group, compounds **128b-d** were treated with 40 molar equivalents of anhydrous 1N HCl in MeOH, produced *in situ* from acetyl chloride and methanol. The mixture of **128a** and **(3R)-128a** was deprotected to the free amino

acid **129a** simply by refluxing in H_2O overnight. The hydrochloride salts of **128b-d** were obtained quantitatively and immediately treated for 20 minutes with a refluxing mixture of excess propylene oxide in EtOH to produce in essentially quantitative yield, the free amino acids coronamic acid (**2**), norcoronamic acid (**3**), and **129d** (Table 3). This procedure works extremely well and obviates the need for ion-exchange chromatography.

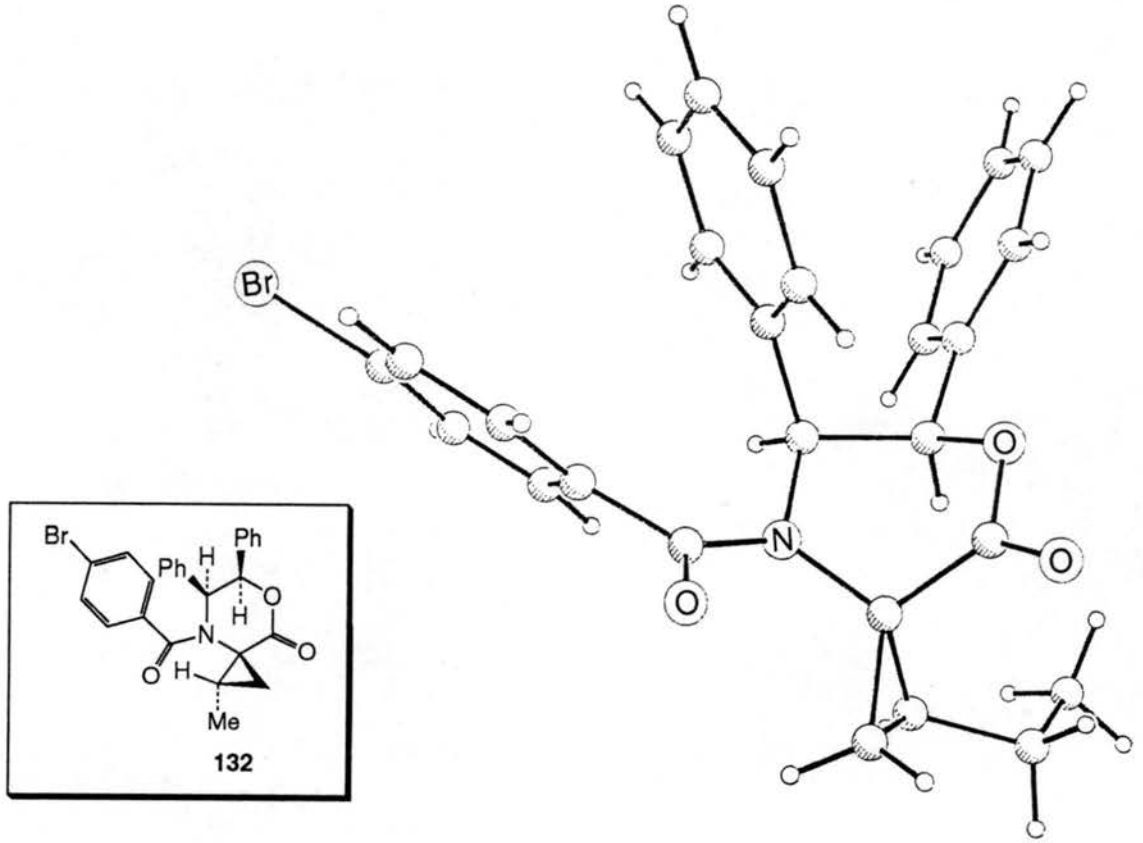
Table 3. Cyclopropane amino acids.

entry	substrate	**128**, % yield	free amino acid, % yield	% ee
1	**127a/(3R)-127a**	**128a/(3R)-128a,** 65.4	**[$^2H_2$]-1**, 100	83.3
2	**127b**	**128b,** 63.2	**3**, 100	>99
3	**127c**	**128c,** 64.4	**2**, 100	>99
4	**127d**	**128d,** 60.9	**129d**, 98.6	>99

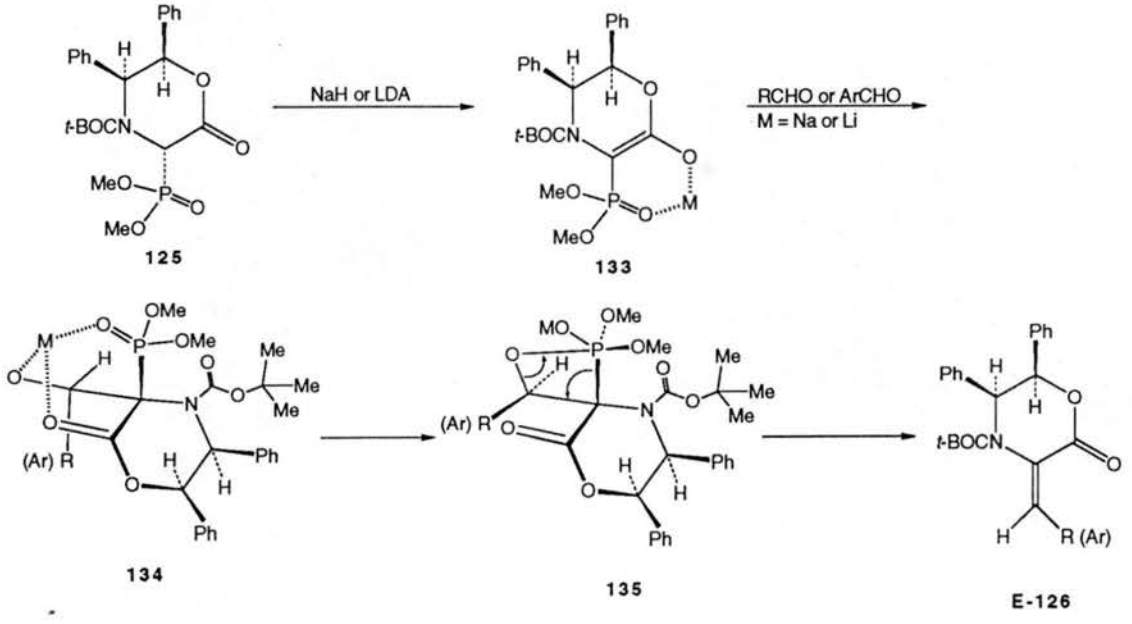
To confirm the absolute stereochemistry of the final cyclopropyl amino acids, assignments were made, in part, by comparing the optical rotations of synthetic coronamic acid (**2**) and norcoronamic acid (**3**) with those reported in the literature.[14b,61] In addition, the relative stereochemistry of the cyclopropyl lactone **127c** was rigorously determined by x-ray analysis of the N-*para*-bromobenzoyl derivative **132** (see experimental section and Figure 12). This structure clearly shows that both the alkene geometry is preserved and that sulfoximine attack on the lactone proceeds from the top (β) face of the double bond. Since the absolute configuration of the lactone systems has been well-established, and presuming that all of the cyclopropanations with the sulfoximine proceed from the top face (β-face, Figure 9) (this is further corroborated by similarities in ^1H NMR behaviour), the stereochemistry of all cyclopropane products (**127-131**) is therefore that depicted in the Schemes.

Several interesting stereochemical points need to be mentioned. The stereoselectivity of the olefination reactions (**125→126**, Scheme 28) is unusual both in the sense of stereochemistry (E-selective) and the complete absence of the Z-isomer. This stereochemical outcome is probably a direct result of the steric interaction between the aldehyde R group and the bulky *t*-BOC protecting group experienced by the two diastereomeric betaine transition states (see **135**, Scheme 30).[54] Generally, it has been observed that condensations involving dialkoxy phosphorylglycine derivatives and aldehydes result in the formation of E/Z-alkene isomeric mixtures with the Z-stereochemistry being predominant.[52d-m] Very recently, Seebach has reported on the preparation of an E-α,β-dehydroamino acid derivative via the phosphoryl condensation approach.[52n]

Figure 12. X-ray stereostructure of the N-*p*-bromobenzoyl derivative **132** prepared from **127c**. Spheres are of fixed, arbitrary radii.



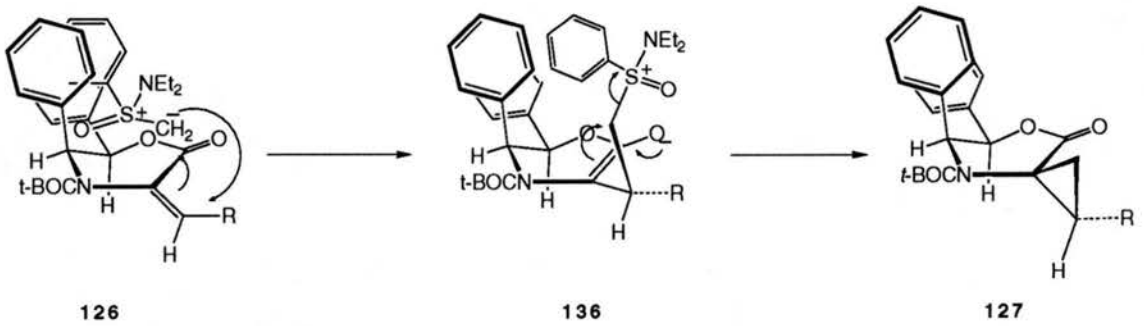
Scheme 30



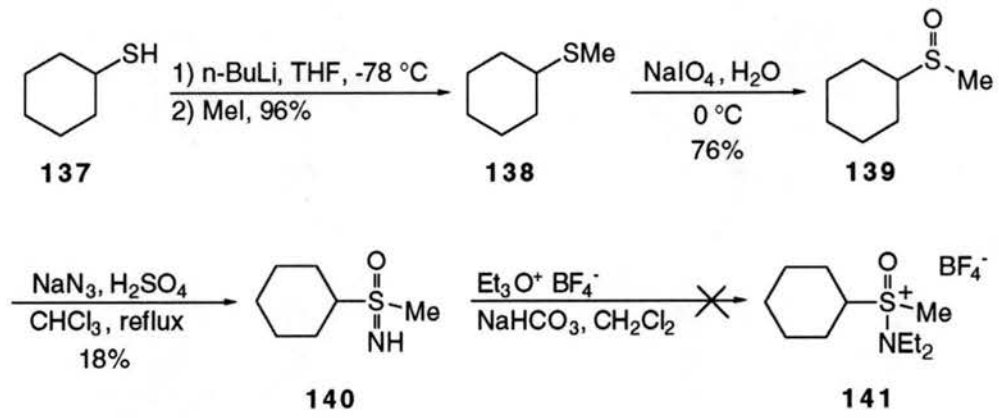
The high degree of facial selectivity of the cyclopropanations with the sulfoximine versus the poorer selectivity of the other cyclopropanating reagents discussed above may be attributable to π-stacking interactions of the phenyl ring of the sulfur ylide and the phenyl rings of the lactone, thus delivering the methylide from the β-face of the double bond (**126**→ **136**, Scheme 31, see also Figure 9). Although this hypothesis is purely speculative, it seemed to be one which could easily be supported by experiment. To this end, a simple study was conducted in which sulfoximine analog **141** containing a cyclohexyl ring would be synthesized and used as a cyclopropanating agent in analogous fashion to that of (diethylamino)phenyloxosulfonium tetrafluoroborate (Scheme 32). The aim in studying the cyclohexyl analog was to see what role the phenyl substituent of the Johnson ylide played in the cyclopropanation reactions. By substituting the phenyl group with a cyclohexyl ring one would anticipate some degree of stereochemical scrambling in the cyclopropanation reaction, if indeed the π-stacking hypothesis was correct. Unfortunately, the sythesis of **141** could not be achieved using the Johnson protocol. The attempted synthesis went as follows: Cyclohexyl mercaptan **137** was treated sequentially with *n*-BuLi and methyl iodide to produce cyclohexyl methyl sulfide (**138**) in essentially quantitative yield. Oxidation of **138** with $NaIO_4$ afforded the corresponding sulfoxide **139** in 76% yield. Treatment of **139** with hydrazoic acid provided unsubstituted sulfoximine **140** in only 18% yield. This was not a surprising result considering the precedented[59f] ease of heterolysis of 2° and 3° alkyl-substituted sulfoximines. Nevertheless, conversion of **140** to the desired (diethylamino)cyclohexyloxosulfonium tetrafluoroborate (**141**) failed and thus precluded the brief mechanistic study.

Examination of molecular models of the putative transition state leading to **136** (see Scheme 31) reveals positioning of the methylide carbon directly over the β-carbon p-orbital. As mentioned above, the x-ray structures[62] of the three α,β-dehydrolactones do not give a convincing impression that either the α- or β-face is significantly shielded sterically, nor is the alkene geometry distorted to any significant extent out of the trigonal plane. One possible explanation is that the ground state conformations of the α,β-dehydrolactones in DMSO are significantly different than those depicted in the x-ray stereostructures. It is conceivable that such conformations could result in steric repulsion between the *t*-BOC group and the C-5 phenyl ring, forcing the *t*-BOC group into a *quasiaxial* position and thus shielding the β-face of the olefin from attack by the methylides. Finally, the fact that no (Z)-cyclopropyllactones **127** were detected in any case, clearly demonstrates that bond rotation about the α- and β-carbon atoms of Michael-type adducts **136** did not occur prior to cyclization to the cyclopropyl product.

Scheme 31



Scheme 32

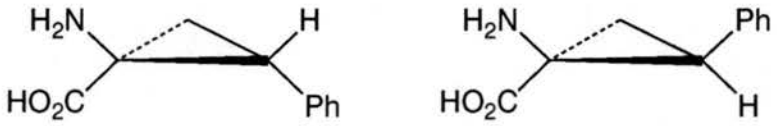


2.2 Asymmetric Synthesis of (1S,2R)-2-Phenyl-1-aminocyclopropane-1-carboxylic Acid

The synthesis of both the (E)- and (Z)-isomers of the unnatural amino acid, 2-phenyl-1-aminocyclopropane-1-carboxylic acid (**142**) (cyclopropylPhe, Figure 13), has been accomplished in racemic fashion.[15e,i-k] To date, only (Z)-cyclopropylPhe has been synthesized in diastereoenriched form;[15q] (E)- and (Z)-cyclopropylPhe have been resolved via the agency of (-)-Brucine,[63] and (-)-*O*,*O*-dibenzoyl tartaric acid,[64] respectively. In recent years there has been considerable interest in the study of peptides that incorporate cyclopropylPhe as a conformationally restricted analog of phenylalanine.[6] This amino acid imposes conformational constraints and hydrolytic stablility on the peptide structure which, may alter the chemical reactivity and molecular recognition properties of the peptide. Continued research in the areas of protein structure

modification[65] and total synthesis[66] may ultimately reveal the full potential of cyclopropylPhe, as well as other ACC derivatives, in medicinal chemistry.

Figure 13

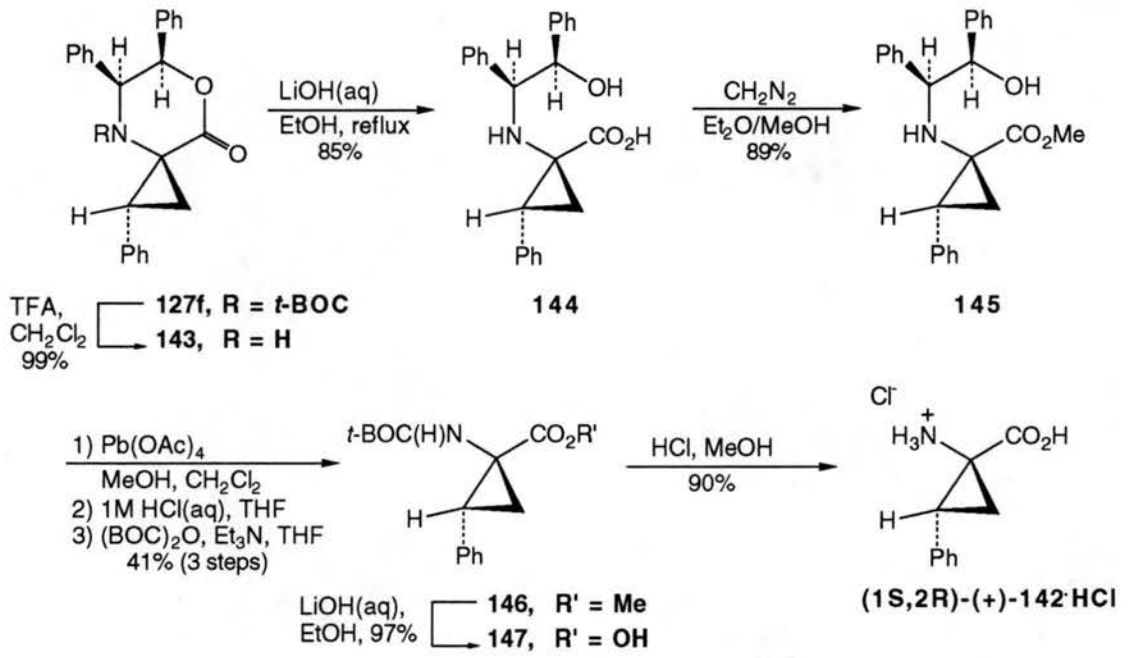


(E)-142 (1S,2R) (1R,2S) **(Z)-142 (1S,2R) (1R,2R)**

In Section 2.1, a method for the asymmetric synthesis of E-selective 2-alkyl-1-aminocyclopropane-1-carboxylic acid derivatives was described. This initial study resulted in the syntheses of (1S)-[$^2H_2$]ACC, (1S,2S)-coronamic acid (**2**), (1S,2S)-norcoronamic acid (**3**), and the unnatural (1S,2S)-2-propyl-1-aminocyclopropane-1-carboxylic acid (**129d**).[67] Unfortunately, the dissolving metal reduction protocol used to generate these amino acids could not be applied to the synthesis of (1S,2R)-2-phenyl-1-aminocyclopropane-1-carboxylic acid[67] (**142**) (cyclopropylPhe, Figure 13), due to the inherent lability[69] of the α,β-cyclopropane bond bearing the phenyl group. In addition, application of a stepwise hydrolysis/periodate cleavage protocol, first described by Weinges[70] on a related heterocycle and employed by Williams and Hendrix[46f] in the synthesis of α-arylglycines from the corresponding α-aryllactones, failed to produce cyclopropylPhe from cyclopropyllactone **127f**. Despite this temporary setback, an alternative stepwise deprotection procedure was sought. Removal of the chiral auxiliary was finally achieved by simply replacing periodic acid with lead tetraacetate,[71] thereby moderating the acidity of the reaction medium. This minor but important change resulted in the first asymmetric synthesis of (1S,2R)-2-phenyl-1-aminocyclopropane-1-carboxylic acid (**142**) in approximately 95% de (Scheme 33).[72]

The synthesis of (1S,2R)-2-phenyl-1-aminocyclopropane-1-carboxylic acid (**142**) began with the TFA-mediated deblocking of cyclopropyl lactone **127f** to amine **143** in essentially quantitative yield, followed by basic hydrolysis of the lactone ring to provide amino acid derivative **144** in 85% yield (Scheme 33). Protection of the carboxyl group using CH_2N_2 afforded methyl ester **145** in 89% yield. The presence of approximately 3% of a minor cyclopropane diastereomer of undetermined absolute stereochemistry was detected in the ^1H NMR spectrum of crude **145**. Since cyclopropyl lactone **127f** is isomerically pure as previously determined,[67] the partial loss of stereochemical integrity

Scheme 33



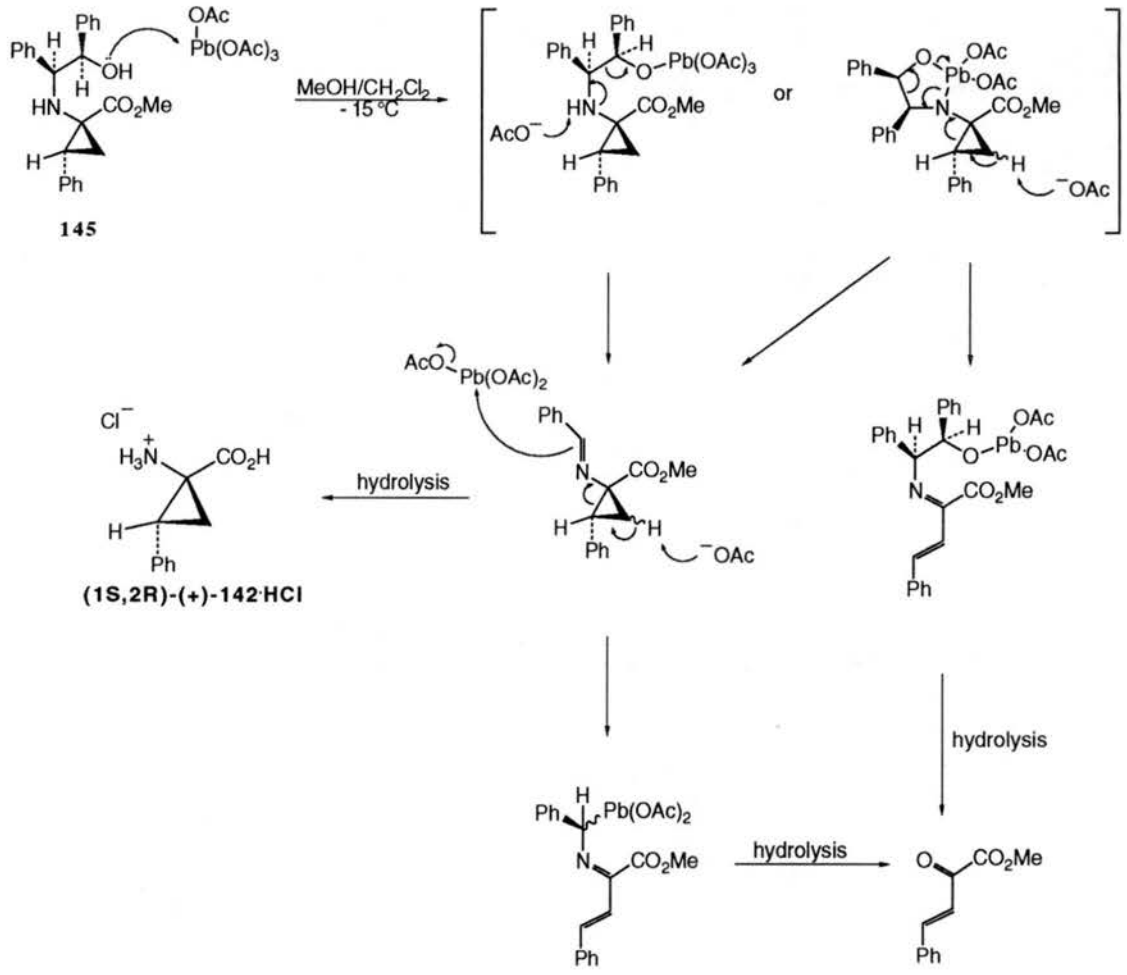
is a result of deprotonation of the amino proton of **143** during saponification, followed by cyclopropane ring opening and reclosure via the corresponding prochiral imine intermediate. A similar decomposition process has been documented in the literature for 1-methyl-2,2-diphenylcyclopropylamine.[73] One possible way to avoid the "stereochemical leakage" observed during the preparation of **144** is to first saponify cyclopropyllactone **127f** prior to removal of the *t*-BOC protecting group.

Cleavage of the chiral auxiliary of **145** was accomplished by using a slight excess of $Pb(OAc)_4$ (LTA) in CH_2Cl_2/MeOH (2:1) at - 15 °C (3 min) to produce the corresponding acid sensitive benzaldehyde imine. The crude imine was immediately converted to the diprotected amino acid **146**[74] in 41% yield via a one-pot sequence that involved acidic hydrolysis followed by nitrogen protection using di-*tert*-butyldicarbonate. It appears that the imine hydrolysis and nitrogen protection reactions of this three step sequence occur in essentially quantitative yield and that the LTA-mediated cleavage reaction is the low yielding step. This is supported by ^1H NMR analyses of both the crude imine and the corresponding cyclopropylPhe methyl ester hydrochloride salt (purified via C_{18} reverse phase chromatography). The ^1H NMR spectrum of the imine intermediate clearly shows major impurities which contain aromatic and olefinic proton resonances. It is likely, although unsupported experimentally, that undesired lead-mediated ring opening pathways are competing during this key oxidative process

(Scheme 34). Several trials of the LTA cleavage reaction were conducted wherein reaction temperature and LTA stoichiometry were altered. Nevertheless, the yield of this process did not increase substantially.

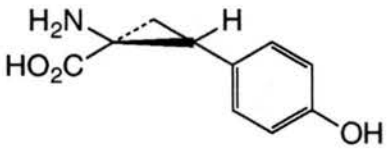
Finally, saponification of methyl ester **146** with LiOH (84 %) followed by deblocking of **147** with anhydrous HCl in MeOH gave (1S,2R)-2-phenyl-1-aminocyclopropane-1-carboxylic acid hydrochloride salt (**142·HCl**) in 78% yield ($[\alpha]_D^{25}$(obsd) = +72.7 ° (c = 1.0, H_2O); $[\alpha]_D^{25}$(lit)[15f] = +74.4° (c = 1.0, H_2O). Subsequent ^{19}F NMR analysis of the Mosher[75] amide of **142** showed the diastereomeric excess to be approximately 95%.

Scheme 34

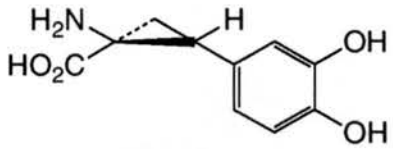


Having successfully converted cyclopropyllactone **127f** to (1S,2R)-cyclopropylPhe **142**, it appeared reasonable to apply the same deprotection strategy to cyclopropyllactones **127h** and **127i**, which would allow for the asymmetric syntheses of cyclopropyltyrosine **148**[76] and cyclopropylDOPA **149**[77], respectively (Figure 14).

Figure 14



148

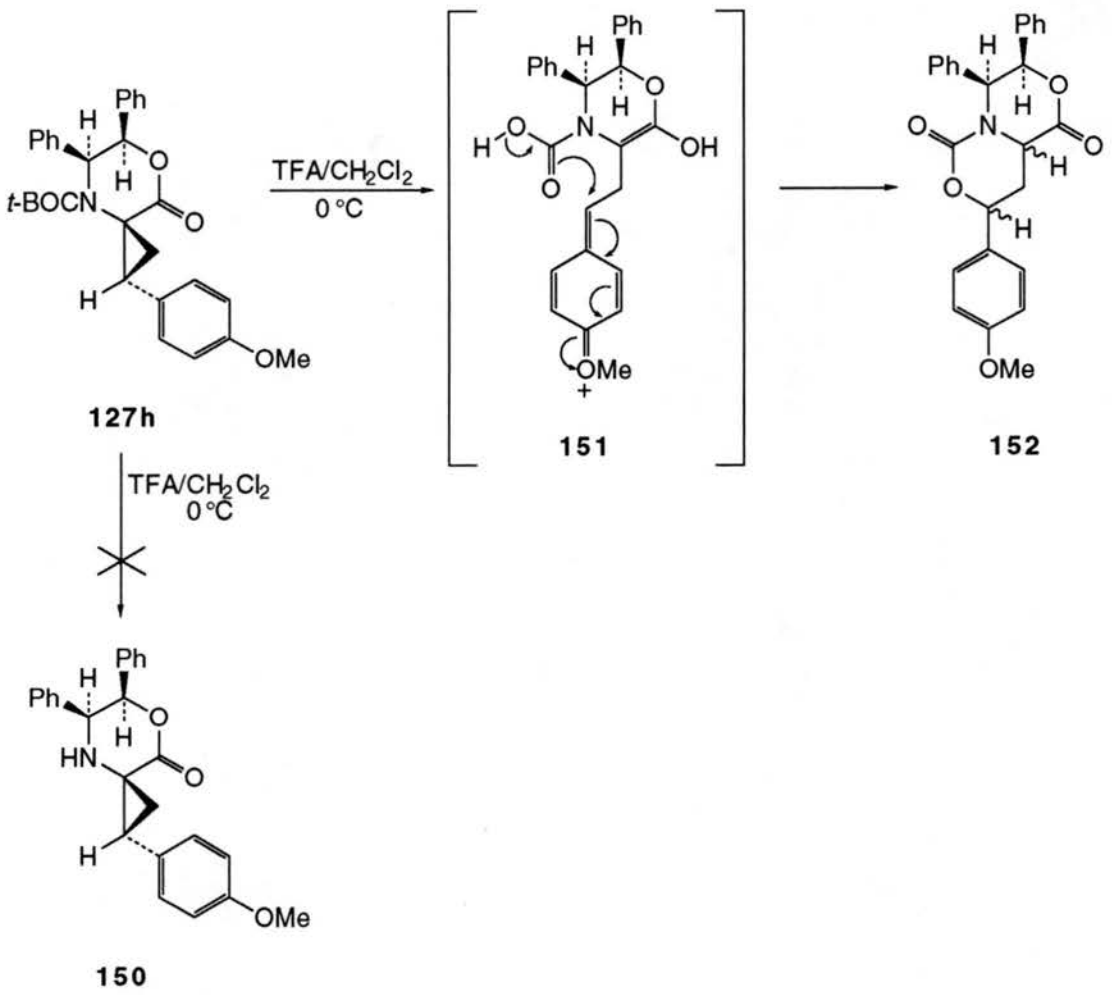


149

Interest in these two amino acids comes from their potential to serve as isosteres of tyrosine and of α-methylDOPA, respectively. For example, tyrosine (Tyr) is found as the N-terminal amino acid of the naturally-occurring analgesic peptide enkephalin. Substitution of Tyr with **148** should lead to an enkephalin analog having increased hydrolytic stability at the Tyr-Gly peptide bond. The structural homology between the tyramine moiety of morphine and the N-terminal tyrosine residue of enkephalin has lead to speculation that the brain binding sites of enkephalin and of morphine might be the same.[79] (E)- or (Z)-Cyclopropyl DOPA **149**, on the other hand, represent conformationally constrained isosteres of the clinically effective antihypertensive drug, α-methyl-3,4-dihydroxyphenylalanine. It might be anticipated that (E)- or (Z)-**149** could serve as an antihypertensive agent in much the same fashion as α-methylDOPA. Based on these facts, it seemed worthwhile to attempt the synthesis of these molecules in an asymmetric fashion.

Following the deprotection sequence outlined for the synthesis of cyclopropylPhe **142** (Scheme 33), cyclopropyllactone **127h** was treated with excess TFA in CH_2Cl_2 at 0 °C. Upon addition of the acid, an instantaneous bright orange color was observed along with the complete consumption of starting material as judged by analytical thin layer chromatography. ^1H NMR analysis of the crude product revealed that the desired amine **150** was not formed (Scheme 35). Instead, the only product isolated after the standard workup was bicyclic urethane **152** as a 5:1 mixture of diastereomers. The absolute and relative stereochemistry of **152** was not determined. This product can be explained mechanistically as arising from: 1) cyclopropane bond rupture at the α,β-bond bearing the *para*-methoxyphenyl substituent in concert with acidolysis of the *tert*-butyl carbamate to form oxonium ion **151**, and 2) ring closure of the carboxyl group of **151** at the γ-carbon, thus producing **152**. This pathway clearly illustrates the enormous effect (electron releasing) that the *para*-methoxy group has on the acid lability of the cyclopropane ring. This problem required that a different deprotection approach be used.

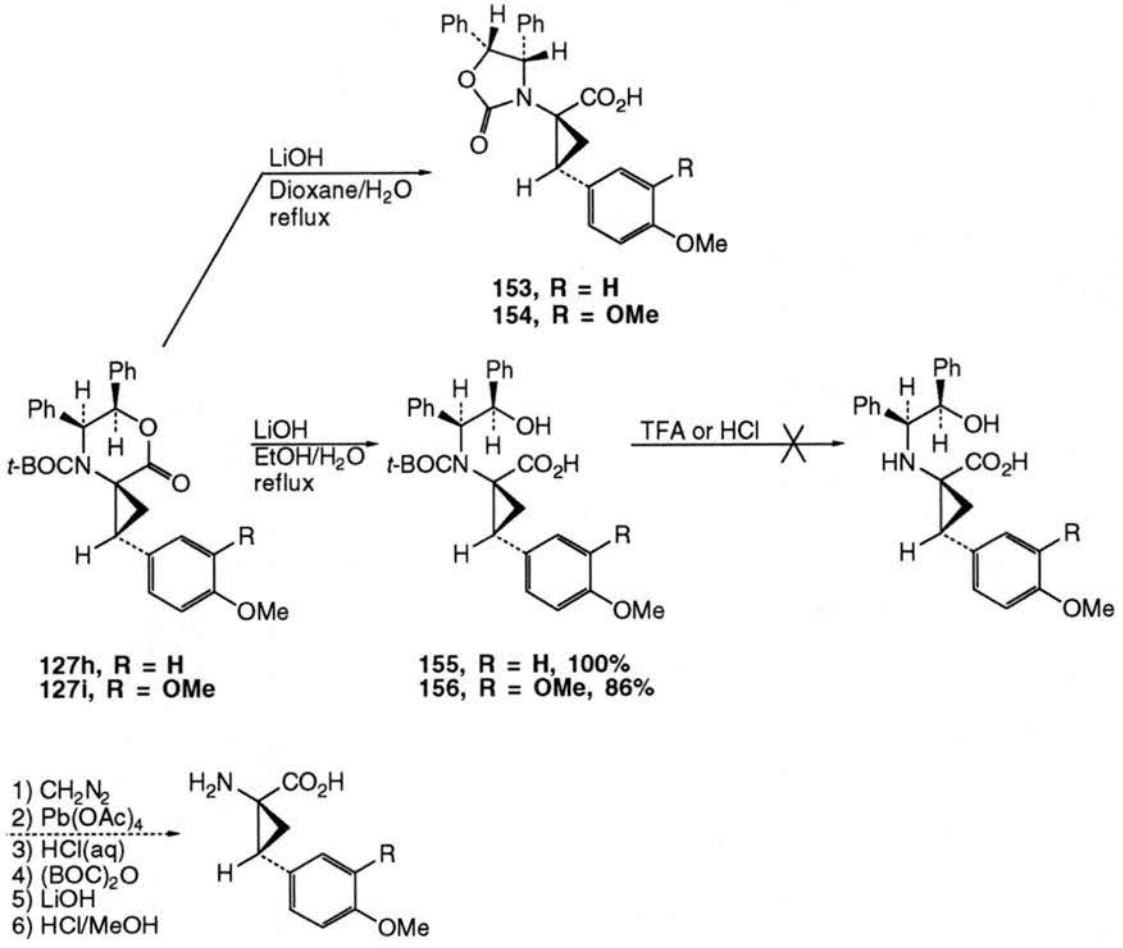
Scheme 35



It was determined that for a successful deprotection of **127h** and **127i** to be realized, lactone saponification would have to precede the acidic removal of the *t*-BOC moiety. In effect, by first opening the lactone ring, one would expect increased stability of the labile α,β-cyclopropane bond due to destabilization of any localized charge about the α-carbon during the undesired cyclopropane fission. Individual treatment of both **127h** and **127i** with aqueous LiOH in refluxing dioxane gave exclusively undesired cyclic carbamates **153** and **154** in high yield (Scheme 36). By substituting dioxane with EtOH, hydroxy acids **155** and **156** were obained as clear oils in quantitative and 86% yields, respectively. Unfortunately, several attempts to remove the *t*-BOC protecting group with trifluoroacetic acid, aqueous HCl, and anhydrous methanolic HCl failed. Trifluoroacetic acid caused extensive decomposition of compound **154** and aqueous HCl reacted only slowly to afford undesired byproducts and recovered starting material. Based on the

racemic synthesis of cyclopropylTyr by Stammer and associates,[76] protection of the phenolic hydroxyl groups of **127h,i** as the (2-methoxyethoxy)methyl (MEM) ethers may be required for the stepwise deprotection protocol to succeed. In consideration of the relative difficulty in purifying α,β-dehydrolactones **126h,i** (see Chapter 3, Experimental) and the poor yield and lower selectivity observed for the cyclopropanation of **126i** (Table 2), this project was regrettably abandoned.

Scheme 36

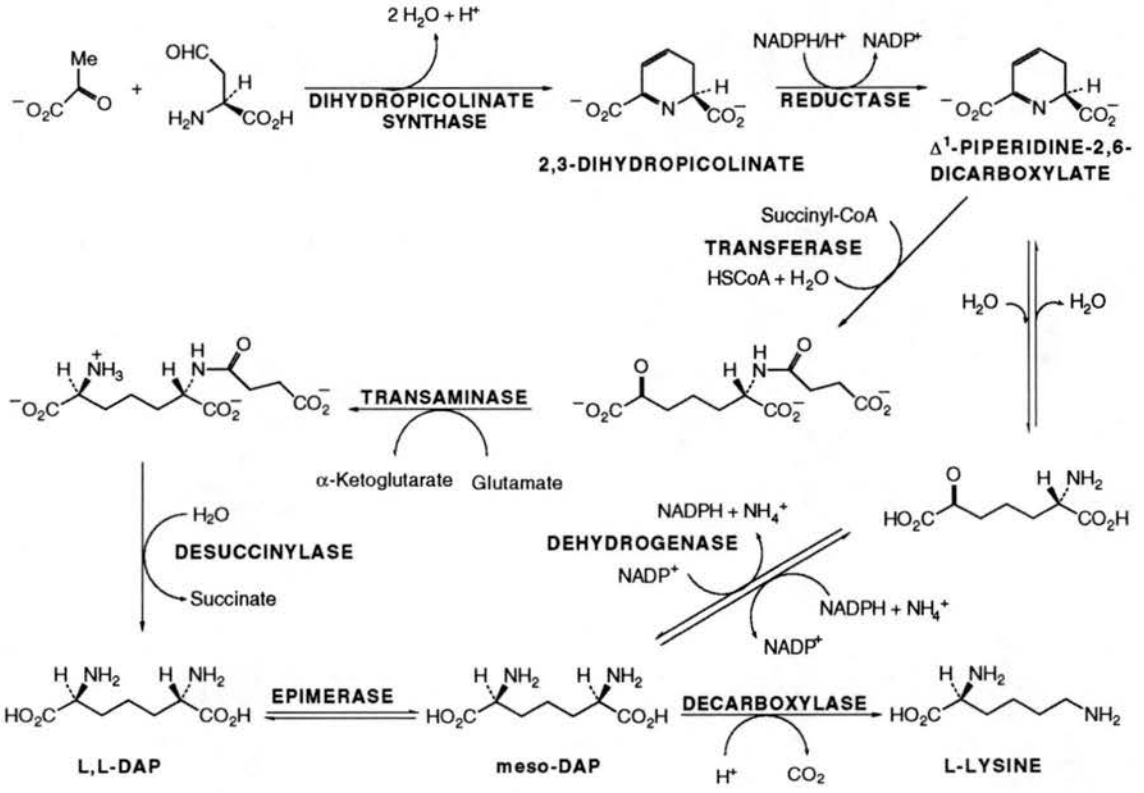


2.3 Asymmetric Syntheses of (2S,3S,6S)-, (2S,3S,6R)-, and (2R,3R,6S)-2,3-Methano-2,6-diaminopimelic Acids

Currently there is growing interest in the design and synthesis of substrate-based inhibitors of any one of the nine enzymes involved in the biosynthetic conversion of pyruvate and aspartate to L-lysine, a process necessary for the metabolic survival of bacteria (Scheme 37). Since mammals lack this pathway and require dietary intake of L-

lysine, it is anticipated that specific inhibitors along this route should perform as potential antibiotics having low host toxicity.

Scheme 37

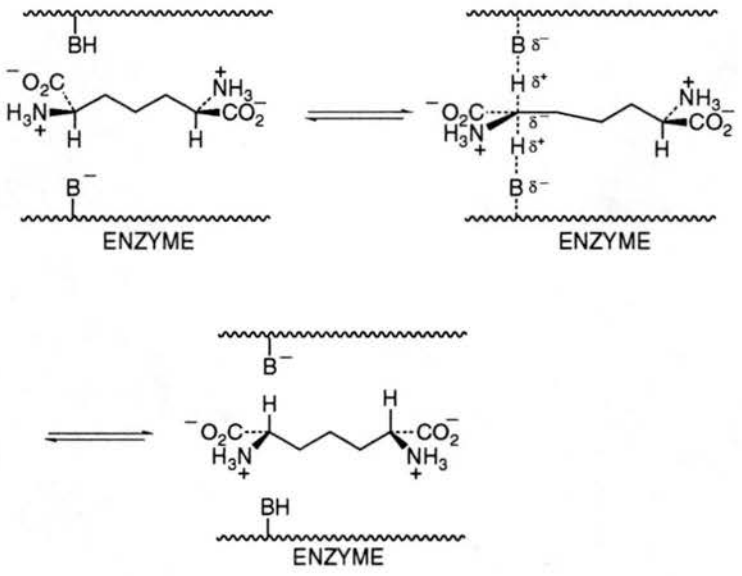


One key enzyme which has commanded much attention in recent years is L,L-diaminopimelate epimerase (EC 5.1.1.7),[79] an unusual enzyme responsible for the interconversion of (L,L)-2,6-diaminopimelic acid to meso-2,6-diaminopimelic acid without the aid of any cofactors such as pyridoxal phosphate. This epimerase enzyme was first discovered in 1957 by Antia and coworkers,[80] and first purified from *Escherichia coli* by Wiseman and Nichols in 1984.[79] The enzyme exists as a monomer having a molecular weight of 34,000 Daltons and is believed to function via a two base in-line deprotonation-protonation mechanism (Scheme 38), much like that of proline racemase.[81] One of the basic residues is believed to be a thiol group based on an experiment in which the enzyme was alkylated and inhibited with iodoacetamide.

The inhibition of meso-DAP metabolism is now an active area of intense research, since this amino acid is a constituent of the cell wall peptidoglycan of virtually all Gram-negative and some Gram-positive bacteria. Peptidoglycan consists of linear sugar chains substituted with short peptide strands which are cross-linked at a D-alanine residue of one

strand and meso-diaminopimelic acid of another via a peptide bond (Figure 15). The sugar chains are composed invariably of alternating N-acetylglucosamine and N-acetylmuramic acid residues. The peptide strands consist of D- and L-configured amino acids and are generally conserved except for the third residue (e.g. L,L-DAP, meso-DAP, or L-lysine), which varies from species to species. Thus reduction or elimination of meso-DAP (or L,L-DAP or L-lysine) from bacteria should result in weakening of the cell wall, subsequent lysis, and finally cell death. Several DAP analogues have been synthesized[82] and studied for epimerase inhibition activity (Figure 16). Most of these analogues (**157**, **158**, **160**, and **161**)[82a,b,d] take advantage of the fact that some anionic character develops on the α-carbon of (L,L)-DAP during the transition state of the epimerase-catalyzed conversion to meso-DAP (see Scheme 38). Thus, appropriate leaving group functionalization of either the amino group or the β-carbon (e.g. hydroxyl- or halosubstitution, respectively) should result in formation of a planar transition state mimic. Therefore, enzyme-catalyzed elimination of HCl (from **157**), HF (from **160** and **161**), or H_2O (from **158**) leads to the common intermediate, dehydro-DAP (**162**).

Scheme 38



In a completely unique approach, racemic aziridino-DAP **159** was prepared and incubated with DAP epimerase and potent irreversible inhibition of the enzyme was observed.[82c] Subsequent tryptic digestion and peptide mapping of the covalently bound enzyme showed that the cysteine 73 residue is labelled,[82d] thus supporting the original proposal of the thiol base (Scheme 39).[79]

Figure 15

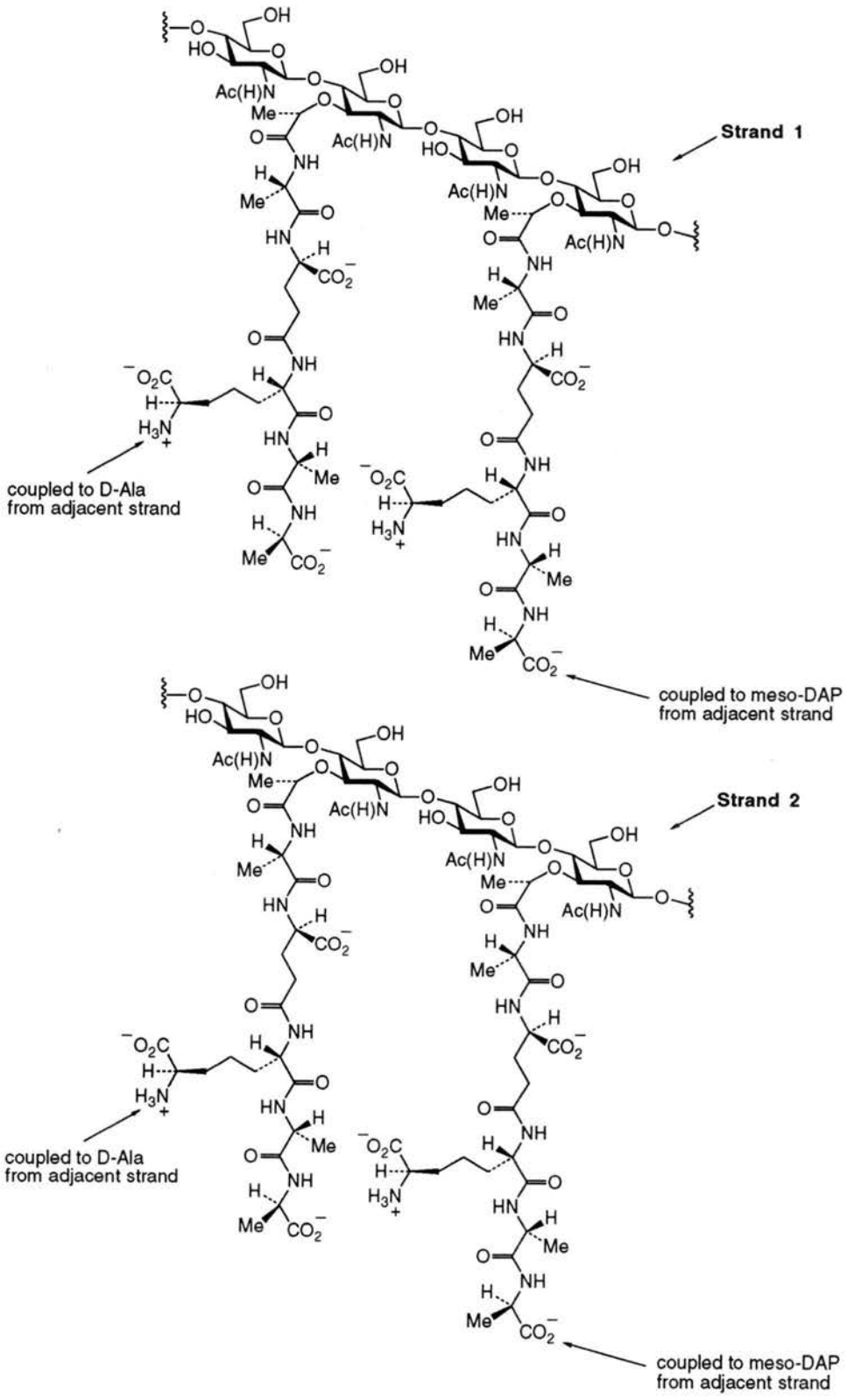
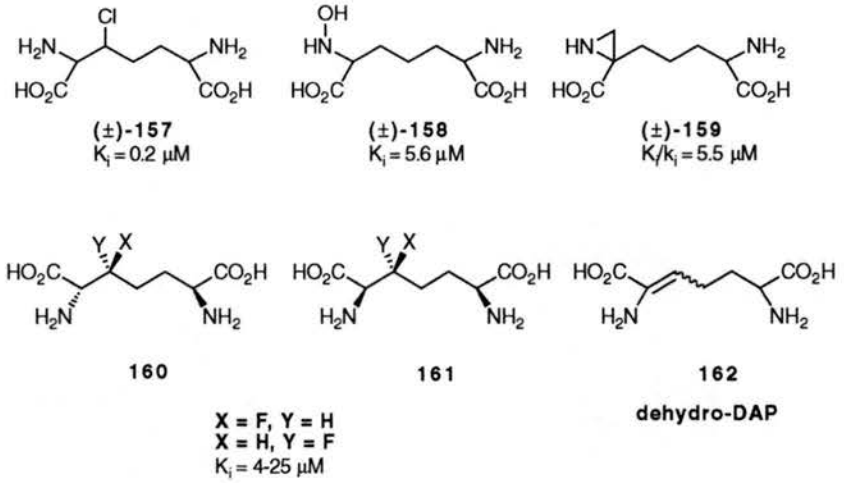
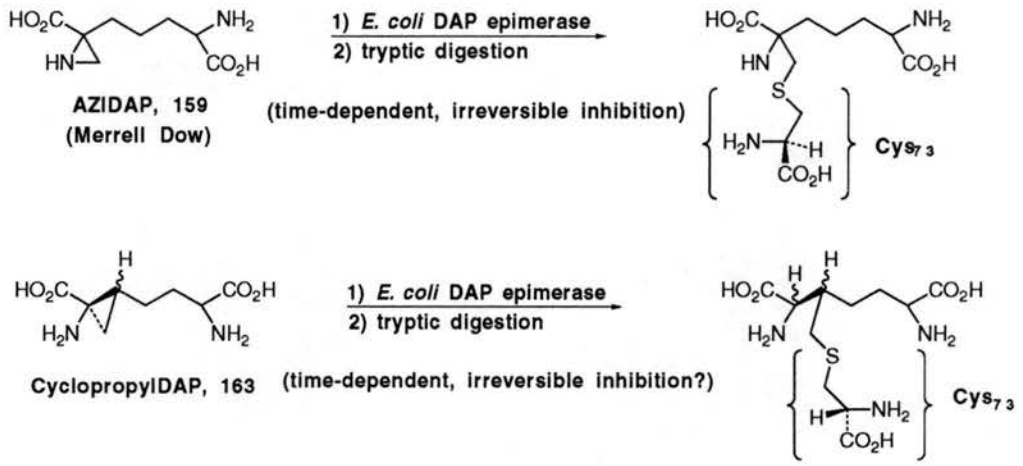

Strand 1
coupled to D-Ala
from adjacent strand
coupled to meso-DAP
from adjacent strand
Strand 2
coupled to D-Ala
from adjacent strand
coupled to meso-DAP
from adjacent strand

Figure 16



Based on the studies involving aziridino-DAP **159** as an electrophilic inhibitor of DAP epimerase, a study was initiated to explore the possibility of using 2,3-methano-2,6-diaminopimelic acid (cyclopropylDAP, **163**) (Scheme 39) as a potential electrophilic inhibitor of the same enzyme. Thus, it was envisioned that attack of the epimerase cysteine thiol upon the cyclopropane group of **163** with concommittant ring opening[83] and release of strain energy would provide the necessary means for possible suicide

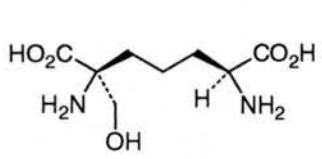
Scheme 39



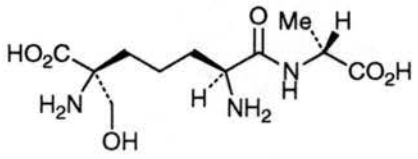
inhibition. During the past few years, the Williams' group has been intensively active in the design and synthesis of diaminopimelate pathway metabolites and inhibitors (Figure 17). Recently, Williams and coworkers[46l] and an Oxford group[46m] have reported the asymmetric synthesis of 2,6-diamino-6-hydroxymethylpimelic acid (**164**) which is a

constituent of the natural antibiotic dipeptide N-(2,6-diamino-6-hydroxymethylpimelyl)-L-alanine (**165**).[84] In addition, Williams and Yuan[85] have successfully accomplished the first asymmetric syntheses of (R,R)-, (S,S)-, and (S,R)-2,6-diaminopimelic acids (**166**) from lactones **112** and **113**. The remainder of this section describes the asymmetric syntheses of (2S,3S,6S)-, (2S,3S,6R)-, and (2R,3R,6S)-2,3-methano-2,6-diaminopimelic acids (cyclopropylDAP, **163**) from chiral non-racemic lactones **112a** and **112b** and the antibiotic properties of these novel DAP analogs. This work is based largely on the methodology previously described in Section 2.1.

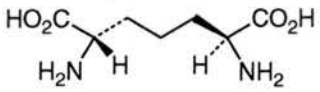
Figure 17



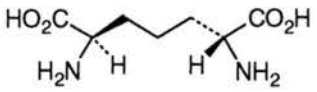
164



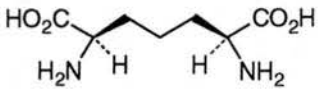
165



L,L-DAP, 166



D,D-DAP, 166



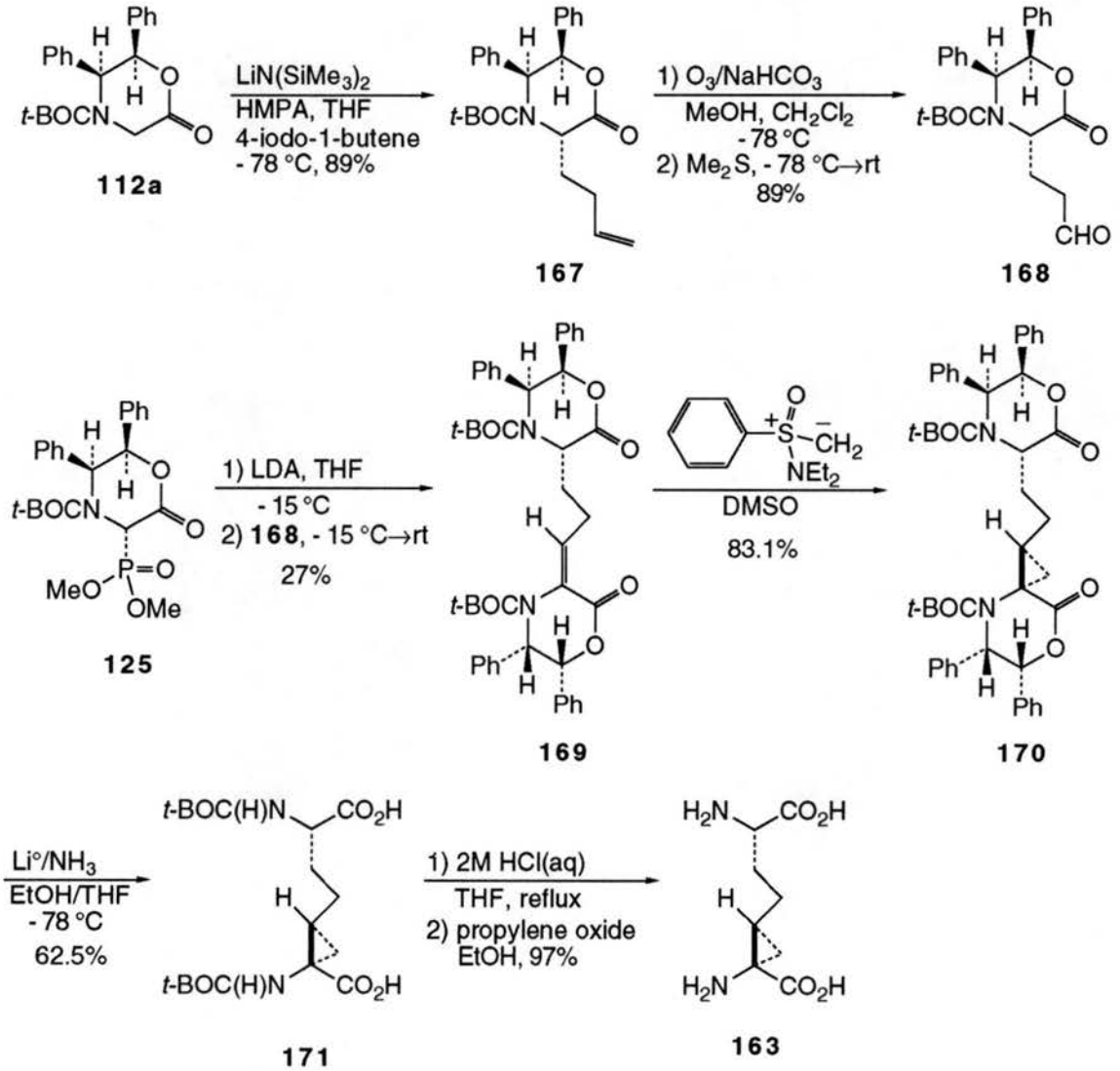
meso-DAP, 166

In order to successfully complete asymmetric syntheses of diastereomeric forms of cyclopropylDAP **163**, two key problems had to be addressed. First, a method was required which would enable the coupling of two optically pure glycinates by a three carbon tether while simultaneously installing α,β-unsaturation to one glycinate terminus in geometrically pure form. Second, a cyclopropanating reagent was needed which could add in a highly stereoselective fashion to the carbon-carbon double bond of the coupled bisglycinate adduct. Once these two critical problems have been solved, the remaining task to finish the synthesis of cyclopropylDAP **163** would simply involve the removal of the chiral auxiliary and deprotection of the nitrogen atoms. The issues of controlling olefin geometry and subsequent facial selectivity in the cyclopropanation reaction have been adequately addressed for the asymmetric syntheses of 2-alkyl-1-aminocyclopropane-1-carboxylic acids (see Section 2.1). It seemed only logical to apply this valuable methodology to the asymmetric synthesis of cyclopropylDAP **163**.

As shown in Scheme 40, the synthesis of cyclopropylDAP **163** began with the preparation of aldehyde **168**[85] and phosphonate ester **125**,[67] the two fragments necessary for constructing the parent backbone. Aldehyde **168** was synthesized in 78% yield by

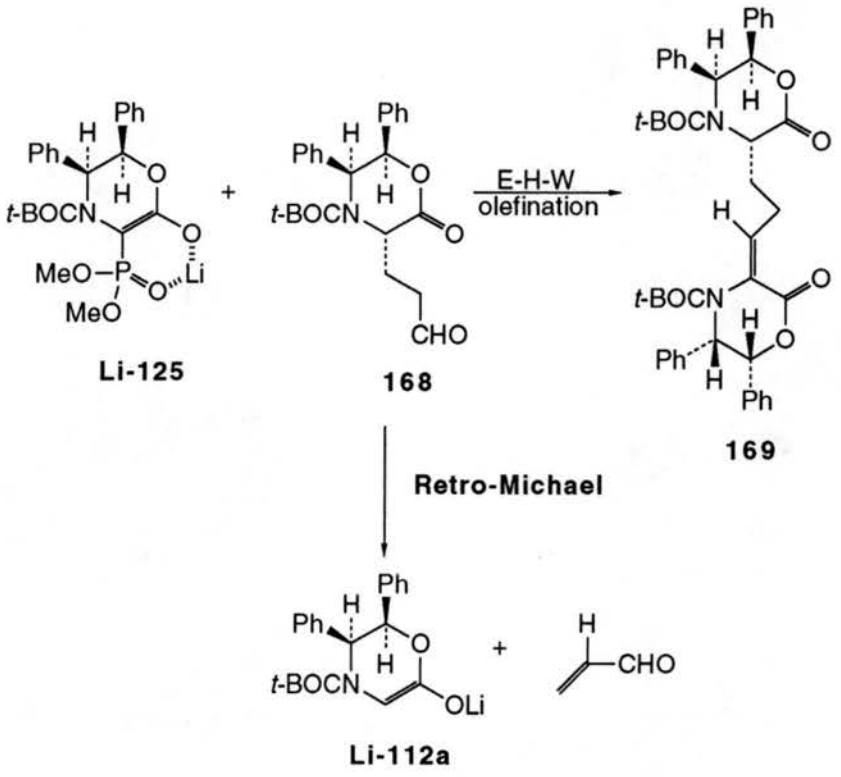
first alkylating the lithium enolate of **112a** with 4-iodo-1-butene followed by ozonolysis of the resulting alkene **167**. Emmons-Horner-Wadsworth condensation of **168** and **125** using LDA as base, provided exclusively (E)-alkene **169** in 27% yield (38% yield based on recovered **125**) as a single diastereomer. Comparison of the crude ^{1}H NMR of **169** with that of α,β-dehydrolactone **126c** gave convincing evidence for the assigned olefin geometry. The best yield of **169** was obtained when a one mole excess of **125** was used in the condensation reaction. The excess and unconsumed portions of **125** could be routinely recovered during flash silica chromatography, whereas in experiments involving excess **168**, attempts to recycle this reagent failed. Not surprising, aldehyde **168** is

Scheme 40



unstable to the basic reaction conditions employed in the condensation process. There is significant evidence (^{1}H NMR) to suggest that the resulting low yield for this key coupling process is due to competitive retro-Michael degradation of aldehyde **168** (Scheme 41). Despite the low yield obtained for the olefination process, efforts to synthesize cyclopropylDAP **163** continued. When alkene **169** was treated with 1.5 equivalents of racemic [(diethylamino)phenyl]oxosulfonium methylide[59,60] in DMSO, cyclopropane **170** was isolated as a single diastereomer[86] in 83% yield. Pure cyclopropane **170** was obtained from the crude material via crystallization from absolute EtOH. Removal of the chiral auxiliary of **170** was accomplished by dissolving metal reduction (Li°/NH_3) to afford the bis *t*-BOC-protected cyclopropylDAP **171** in 62.5% yield. Deblocking of the *t*-BOC groups using HCl(aq) followed by conversion of the corresponding HCl salt to free (2S,3S,6S)-2,3-methano-2,6-diaminopimelic acid **163** with propylene oxide was accomplished in 97% yield.

Scheme 41

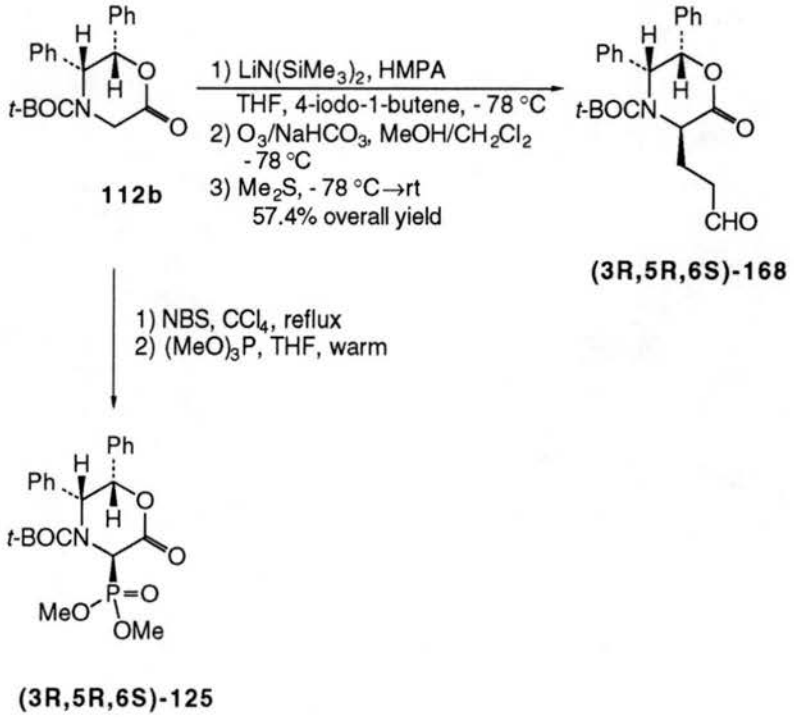


The synthesis of (2S,3S,6S)-2,3-methano-2,6-diaminopimelic acid **163** was achieved entirely from lactone **112a**. The opportunity now existed to apply the same methodology to the synthesis of the (2S,3S,6R)- and (2R,3R,6S)-isomers of cyclopropylDAP **163** (isosteric analogs of D,L- and L,D-DAP, respectively) using a

combination of both antipodes of **112**. The purpose of this exercise was to ascertain any possible specificity by the DAP epimerase active site towards binding of these novel DAP analogs. It was unclear which cyclopropylDAP diastereomer, if any, the epimerase would bind and potentially process. The (2R,3R,6R)-diastereomer of **163** was not considered in this preliminary investigation, since it represented an unnatural "D,D-configured" 2,6-diaminopimelic acid and is not expected to be processed by the enzyme.

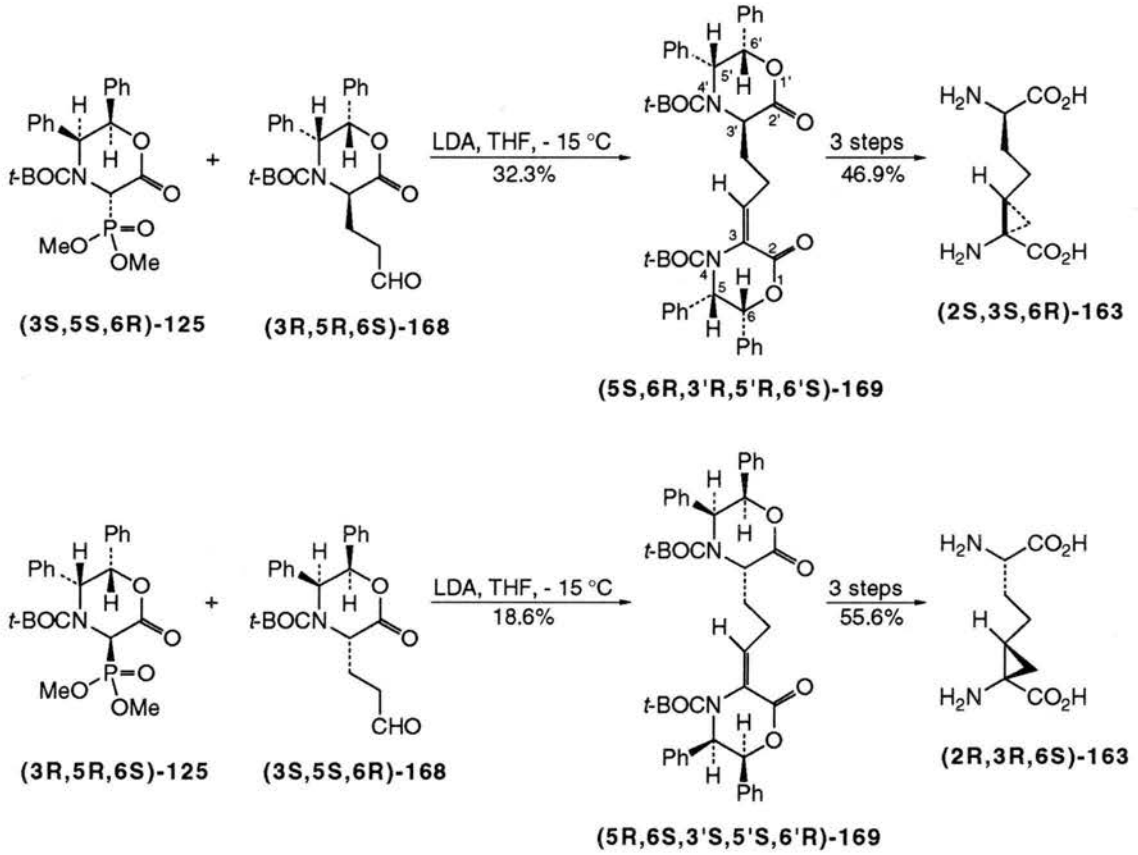
The synthesis of (2S,3S,6R)- and (2R,3R,6S)-2,3-methano-2,6-diaminopimelic acids **163** first required the synthesis of (3R,5R,6S)-**168** and (3R,5R,6S)-**125** from lactone **112b** (Scheme 42). As anticipated, the preparation of these intermediates occurred uneventfully and the spectroscopic data matched identically with the enantiomorphs in every respect, except for the sign of the respective optical rotation values. The remaining task simply involved the couplings of **(-)-125** with **(+)-168** and **(+)-125** with **(-)-168** to afford the desired "D,L- and L,D-diastereomers" of cyclopropylDAP according to the protocol described above. Again, the Emmons-Horner-Wadsworth reaction involving enantiomeric forms of **125** and **168** resulted in low yields of alkene **169**. Fortunately, both olefin diastereomers were obtained in geometrically pure form (i.e. E-selective) as illustrated in the first example (see Scheme 40). A summary of the syntheses of (2S,3S,6R)- and (2R,3R,6S)-cyclopropylDAP **163** is shown in Scheme 43.

Scheme 42



Having a moderately successful synthesis of cyclopropylDAPs **163** in hand, the final segment of the program involved a two phase screening of these novel analogs for antibacterial activity. First, the three diastereomers of **163** were individually tested against Gram (+) bacteria (*Bacillus subtillis*, *Staphyllococcus aureus*, *Micrococcus luteus*), Gram (-) bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Pseudomonas aeruginosa*), and Yeast (*Candida albicans*, *Saccharomyces cerevisiae*) using the agar-paper disc diffusion technique (Table 4). All microorganisms showed complete resistance to the cyclopropylDAP derivatives between concentrations of 0.1 mg/mL and 10 mg/mL. These results, although disappointing, do not completely rule out

Scheme 43



inhibition properties of **163** towards the epimerase enzyme, since the efficacy of drug transport across the bacterial (and Yeast) membranes cannot be ascertained from these strictly qualitative experiments. A more rigorous set of experiments would require incubation of cyclopropylDAPs **163** with purified epimerase to unambiguously determine activity profiles.

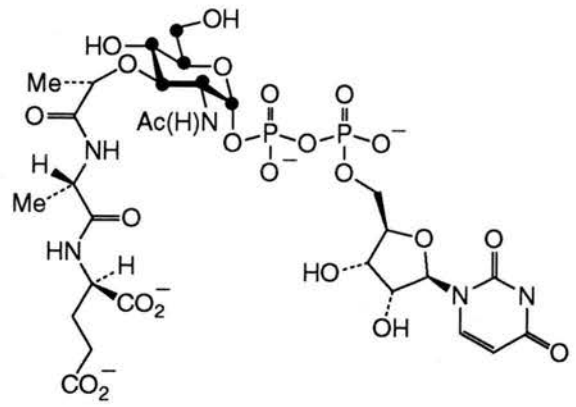
Table 4. Antimicrobial Assays for CyclopropylDAPs **163**.

	Concentration of **(2S,3S,6S)-, (2S,3S,6R)-,** or **(2R,3R,6S)-cyclopropylDAP 163**				
Microorganism	10 mg/mL	1 mg/mL	0.1 mg/mL	10 μg/mL	1 μg/mL
Bacillus subtilis	R	R	R	R	R
Staphylococcus aureus	R	R	R	R	R
Micrococcus luteus	R	R	R	R	R
Escherichia coli	R	R	R	R	R
Klebsiella pneumoniae	R	R	R	R	R
Serratia marcescens	R	R	R	R	R
Pseudomonas aeruginosa	R	R	R	R	R
Candida albicans	R	R	R	R	R
Sacchromyces cerevisiae	R	R	R	R	R

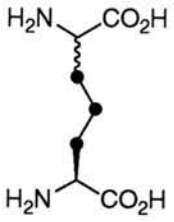
R = Resistance against drug; growth of microorganism up to disc.

The second antibacterial screening program examined in this study involved a peptidoglycan synthesis assay in which ether-treated *E. coli* strain K12 JE5707 was used. These experiments were conducted in the laboratories of Dr. David L. Pruess of Hoffmann-LaRoche, Inc. The procedure involved the incubation of the microorganism with uridine diphospho-N-acetylmuramyl-L-Ala-D-Glu, meso- or L,L-DAP, D-Ala-D-Ala, and cyclopropylDAP **163** added to the reaction medium (Scheme 44). The extent of subsequent uridine diphospho-N-acetylmuramyl pentapeptide (a monomeric unit of peptidoglycan) formation was analyzed with the aid of radiolabelled substrates, meso-2,6-diamino (3,4,5-^{3}H) pimelic acid or uridine diphospho[^{14}C]-N-acetylglucosamine. When meso-2,6-diamino (3,4,5-^{3}H) pimelic acid was added to the reaction, (2S,3S,6S)-cyclopropylDAP **163** (IC_{50} = 8.4 mM) appeared to inhibit peptidoglycan (PG) synthesis to a slight extent (Table 5). Since (2S,3S,6S)-**163** is isosteric to L,L-DAP, it was reincubated using L,L-DAP or meso-DAP with UDP[^{14}C]-N-acetylglucosamine as the radiolabelled substrate. (2S,3S,6S)-CyclopropylDAP **163** stimulated PG synthesis when 50 μM L,L-DAP was used as the substrate (168% of control at 10mM), but had essentially no effect when 50 μM meso-DAP was used (Table 6). These results contradict the previous finding that (2S,3S,6S)-cyclopropylDAP **163** at 10mM concentration, inhibited PG synthesis. This peculiarity can be rationalized if (2S,3S,6S)-cyclopropylDAP **163** behaves as a substrate for the DAP-ligating enzyme. As a substrate, (2S,3S,6S)-**163** competes with the radiolabelled meso-DAP. Thus the reaction should produce less radioactively labelled peptidoglycan. The fact that there is no net

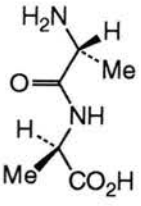
Scheme 44



UDP-MurNAc-L-Ala-D-Glu



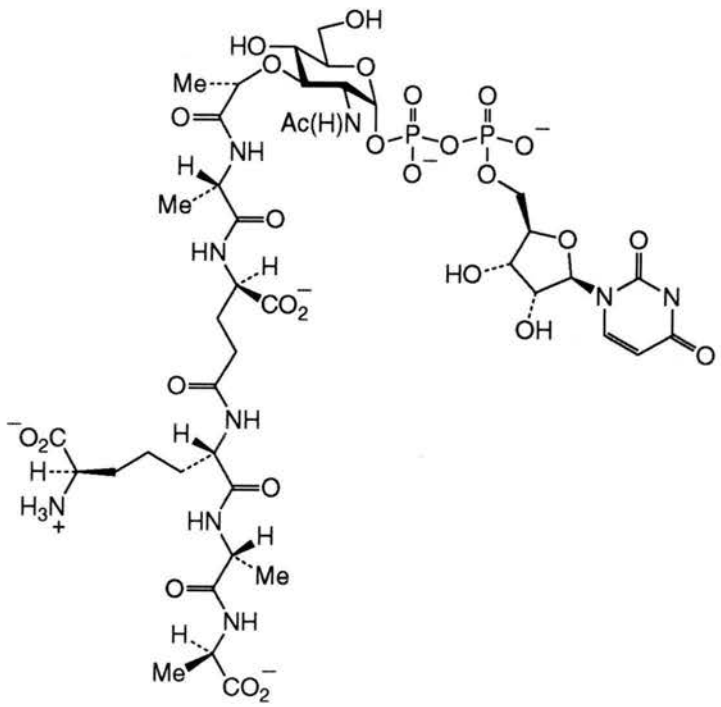
D,L- or L,L-DAP



D-Ala-D-Ala

(•) represents positions of ^{14}C labelling on the glucosamine ring and positions of ^{3}H labelling on meso- or L,L-DAP

E. coli K12 JE5707 incubated with (2S,3S,6S)-**163**



UDP-N-MurNAc-L-Ala-D-Glu-(D,L)-DAP-D-Ala-D-Ala

increase in PG synthesis when (2S,3S,6S)-**163** is combined with meso-DAP and UDP[^{14}C]-N-acetylglucosamine, suggests that meso-DAP is a better substrate for the DAP-ligating enzyme than is (2S,3S,6S)-cyclopropylDAP **163**. The hypothesis that (2S,3S,6S)-**163** behaves as a substrate to the DAP-ligating enzyme was confirmed by testing the compound in the PG synthesis assay in the absence of DAP (Table 7). Also, it does not appear that cyclopropylDAP **163** is an inhibitor of DAP epimerase, since PG synthesis is stimulated, not inhibited, when L,L-DAP is present in the reaction medium. In similar fashion, (2R,3R,6S)-cyclopropylDAP **163** was also found to be a substrate of the DAP-adding enzyme and appeared to only slightly inhibit PG synthesis when incubated with radiolabelled meso-DAP while slightly increasing PG synthesis when incubated with radiolabelled UDP-N-acetylglucosamine. (2S,3S,6R)-CyclopropylDAP **163** was not tested in the permeabilized *E. coli*-mediated peptidoglycan synthesis assay system.

Table 5. Peptidoglycan synthesis assay using (meso)-2,6-diamino-3,3,4,4,5,5-hexatritio-pimelic acid as radiolabelled substrate.

compound	concentration	% inhibition
(2S,3S,6S)-**163**	10 mM	53
(2S,3S,6S)-**163**	1 mM	12
(2S,3S,6S)-**163**	0.1 mM	0

Table 6. Peptidoglycan synthesis assay using UDP[^{14}C]-N-acetylglucosamine as radio-labelled substrate.

compound with 50 μM L,L-DAP:	concentration	% of control
(2S,3S,6S)-**163**	10 mM	168
(2S,3S,6S)-**163**	1 mM	123
(2S,3S,6S)-**163**	0.1 mM	108
with 50 μM D,L-DAP:		
(2S,3S,6S)-**163**	10 mM	104
(2S,3S,6S)-**163**	1 mM	107
(2S,3S,6S)-**163**	0.1 mM	102

Table 7. Peptidoglycan synthesis assay without meso- or L,L-DAP.

compound	concentration	% of control	pmole incorporation
(2S,3S,6S)-**163**	10 mM	101	59
(2S,3S,6S)-**163**	1 mM	59	35
(2S,3S,6S)-**163**	0.1 mM	11	7

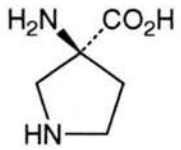
The control reaction mixture contained 50 μM meso-DAP.

2.4 Asymmetric Synthesis of (S)-(-)-Cucurbitine

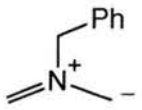
Cucurbitine (**172**), shown in Figure 18, is a naturally occurring amino acid found in the seeds of several *Cucurbita* (pumpkin) species and is known to inhibit the growth of immature *Schistosoma japonicum*. It was first isolated from *Cucurbita moschata* by Fang and coworkers[87] and the absolute stereochemistry was later determined to be of the (S)-configuration.[88] To date there exists only two racemic syntheses[89] and one enantiospecific synthesis[90] of the title compound. The enantiospecific synthesis of (S)-(-)-cucurbitine (**172**) was accomplished by a method involving 1,3-dipolar cycloaddition of azomethine ylide (**173**)[91] (derived from N-benzyl-N-(methoxymethyl)trimethylsilyl-methylamine) to diethyl methylenemalonate (Scheme 45). Subsequent pig liver esterase-catalyzed hydrolysis of the pro-(R) ester group followed by conversion of the free carboxylate to an amino group via the Curtius rearrangement, provided the cucurbitine nucleus. The maximum observed enantiomeric excess for the esterase hydrolysis reaction was only 10%.

Considering the general lack of successful asymmetric syntheses of cucurbitine and structurally related derivatives, it seemed to be a relatively trivial task to apply the axially chiral α,β-dehydroalanine amino acid methodology[46n] to this challenging problem. Accordingly, α,β-dehydrolactone derivatives **126a-i** can potentially serve as suitable substrates for the development of other stereoselective cycloaddition processes (i.e. dipolar cycloaddtions and Diels-Alder transformations). As mentioned earlier, addition of diazomethane to **126a** and **126b** resulted in the formation of diastereomeric pyrazolines, and subsequently the corresponding cyclopropanes, in approximately a 2-3:1 ratio in which *anti* addition predominated. The poor stereoselectivity of this process was discouraging initially, however, it was rationalized that CH_2N_2 reacts too rapidly to discriminate between the α- and β-faces of the olefin substrate. When diphenyldiazomethane was used as the 1,3-dipole, increased selectivity (6.2:1) was observed. This modest increase in selectivity can be explained in two ways. First, the increased bulk of this reagent creates a sterically congested environment during approach

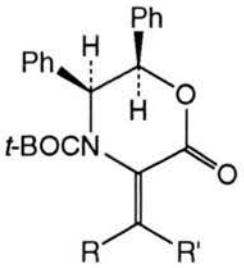
Figure 18



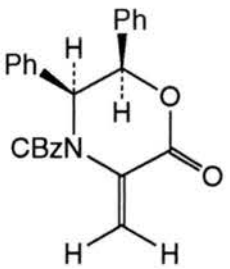
S-(-)-Cucurbitine, 172



173

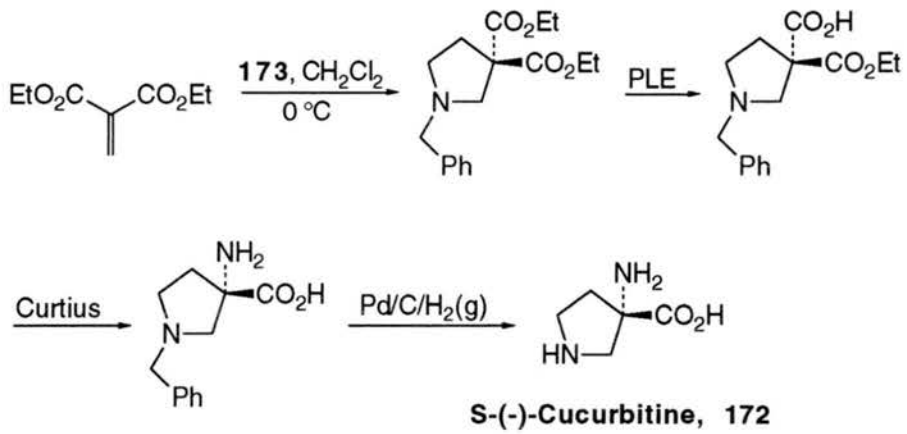


126a: R = R' = ^{2}H
126b,c,f: R = H; R' = Me, Et, Ph



174

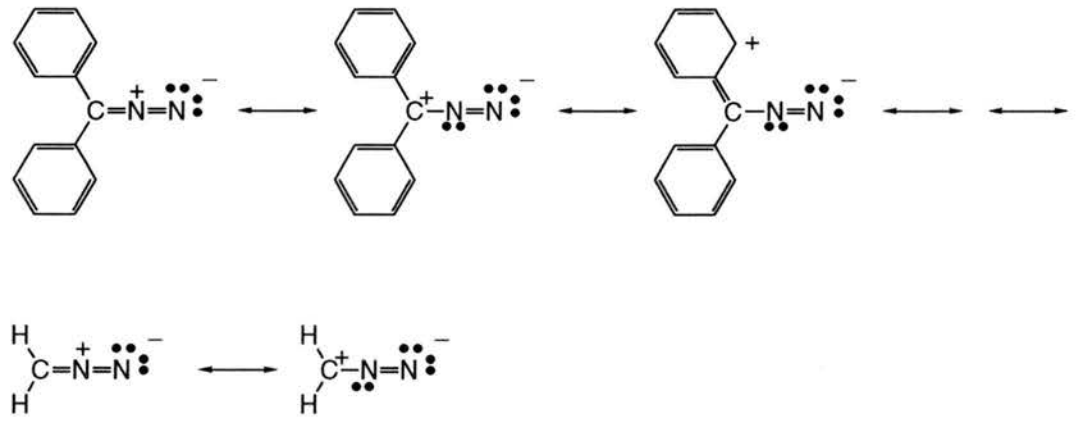
Scheme 45



S-(-)-Cucurbitine, 172

of the β-face of the olefin; thus, interaction between the reagent and the C-5 and C-6 phenyl groups is predicted to be disfavorable. It is assumed that the reaction occurs preferentially from the α-face, although the relative stereochemistry of the cyclopropane product has not been rigorously assigned. Secondly, it is expected that the ground state of diphenyldiazomethane, relative to diazomethane, is considerably lower in energy based on resonance stabilization (Figure 19). Therefore, diphenyldiazomethane reacts slower

Figure 19

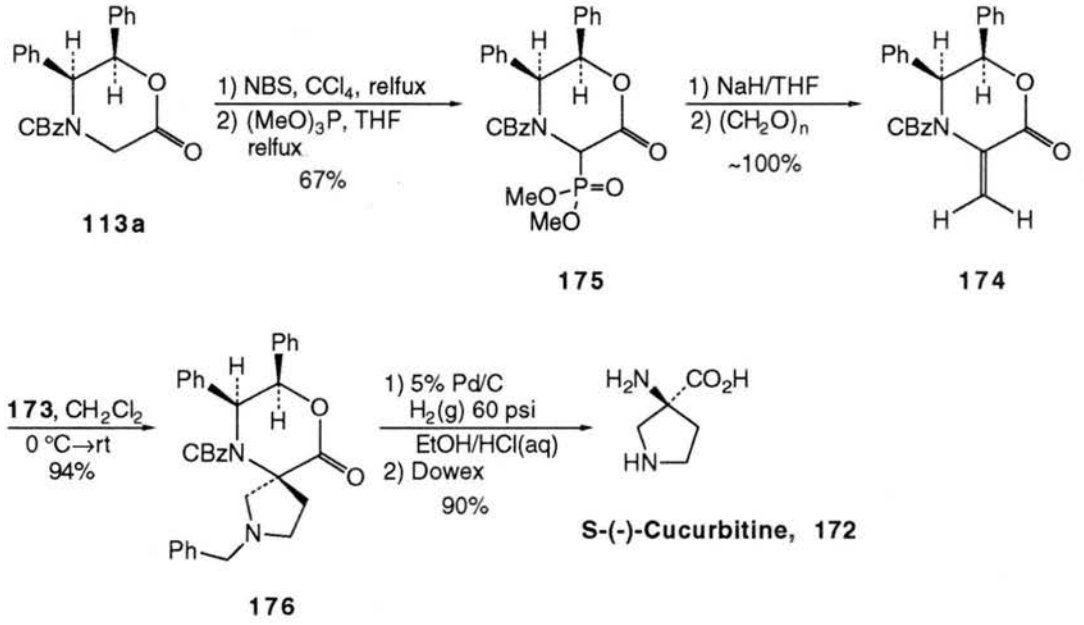


than CH_2N_2 and discriminates more effectively between the two faces of the olefin, although only modestly in the present case. For the synthesis of cucurbitine (**172**), the plan involved 1,3-dipolar cycloaddition of azomethine ylide **173** to α,β-dehydrolactone derivative **174**, since deprotection to the requisite amino acid would only require a one-step hydrogenolysis of the newly formed cycloadduct **176** (Scheme 46). Based on the stereoelectronic considerations described above for diphenyldiazomethane and diazomethane, it was anticipated that azomethine ylide **173** would exhibit facial selectivity intermediate between the two 1,3-dipole cyclopropanating reagents. Surprisingly, azomethine ylide **173** performed beyond these expectations.

The stereoselective synthesis of (S)-(-)-cucurbitine (**172**) went according to the following procedure:[92] Lactone **113a** was readily converted to phosphonate ester **175** in 67% yield and subsequently to α,β-dehydrolactone (**174**, quantitative) as described earlier[67] for the synthesis of the corresponding N-*t*-BOC-protected analogues. Treatment of **174** with **173** (generated *in situ* from 5.0 equiv of N-benzyl-N-(methoxymethyl)[(trimethyl)silyl]methylamine and 0.2 equiv TFA)[91a] in CH_2Cl_2 between 0 °C and room temperature, provided pyrrolidine **176** in 94% yield after crystallization of the crude product from EtOH. Compound **176** was obtained as a single diastereomer as determined by examination of the ^1H NMR of the crude product. Finally, (S)-(-)-cucurbitine (**172**) was obtained in 90% yield by treating an EtOH solution of **176** with 0.1 equiv 5% Pd/C, 3.0 equiv HCl(aq), and H_2(g) at 60 psi for 12 hours. The free amino acid was obtained by sequentially eluting an aqueous solution of the crude HCl salt on a C_{18} Sep-pak cartridge and a Dowex cationic ion exchange column. The optical purity of the synthetic cucurbitine was determined by optical polarimetry and Mosher amide analysis and are consistent with reported data. It is interesting to note that

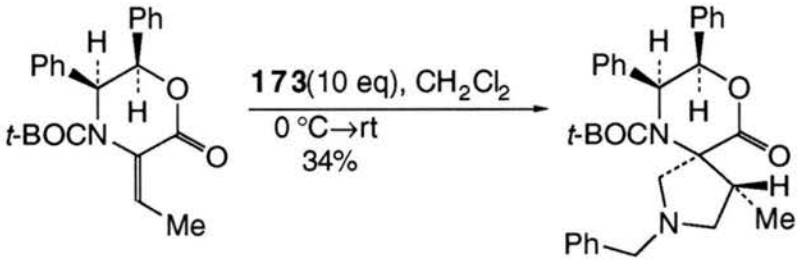
the high degree of facial selectivity for the azomethine ylide addition to **174** contrasts our previous diazomethane cycloadditions with similar olefin substrates.[67] Again this is an inherent result of the slower reacting and thus more discriminating azomethine ylide **173**.

Scheme 46

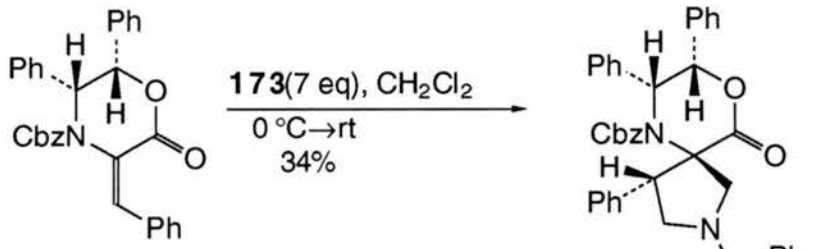


Attempts to synthesize unnatural cucurbitine analogs clearly illustrated the limitations of this methodology. For example, addition of azomethine ylide **173** to α,β-dehydrolactones **126b** and **179** resulted in the production of diastereomerically pure pyrrolidines **178** (34%) and **180** (34%), respectively (Scheme 47). Unfortunately, the yields of these reactions could not be increased by simply adding more ylide. The major problem with these cycloaddition reactions is that dimeric (1,4-dibenzylpiperazine) and oligomeric forms of ylide **173** are produced in competition with the desired cycloadducts. It appears that azomethine ylide oligomerization occurs faster kinetically than the cycloaddition of the ylide to the more sterically hindered α,β-dehydrolactones (**126b** and **179** versus the less hindered **174** in Scheme 46). This undesired kinetic partitioning is further amplified as the net concentration of α,β-dehydrolactone substrate decreases as the reaction progresses. The large quantities of oligomeric **173** produced in the cycloadditon reactions greatly hampered the purification of pyrrolidines **178** and **180**. Typically, two or three rounds of flash silica chromatography and/or preparative thin layer chromatography were required to produce highly pure cycloadducts. Despite the excellent diastereofacial selectivities observed in the ylide addition reaction, no further attempts were made to synthesize unnatural cucurbitine analogs.

Scheme 47



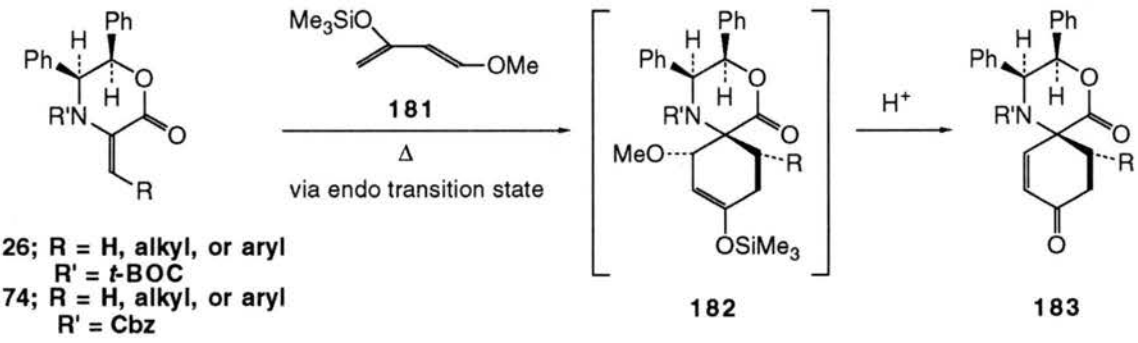
126b **178**

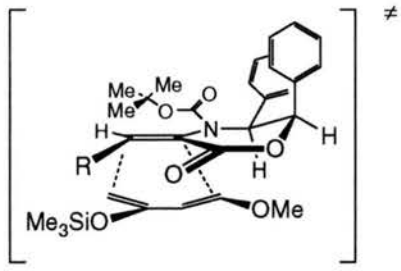


179 **180**

Finally, some brief comments should be made regarding preliminary experiments involving α,β-dehydrolactones in Diels-Alder cycloaddition reactions. At the outset, it seemed likely that the high diastereofacial selectivity observed for azomethine ylide additions to α,β-dehydrolactones should also be realized in Diels-Alder cycloadditions, provided that a diene with suitable electronic characteristics was chosen. Arguably, the carbon-carbon double bond of the α,β-dehydrolactones described in this chapter is electron deficient; this is based on the reactivities displayed with 1,3-dipoles. The lactone carbonyl group exerts an electron-withdrawing effect on the carbon-carbon double bond and thus outweighs the weak electron-donating capability of the lactone nitrogen atom which is in resonance with the urethane carbonyl. Therefore an electron rich diene is necessary for a successful [4π + 2π] cycloaddition with a dienophile such as an α,β-dehydrolactone, especially if Lewis acids are to be avoided. The concern here was that the lactone ring and *t*-BOC protecting group are reasonably unstable to Lewis acids and that avoidance of these Diels-Alder catalysts would result in cleaner reactions. Based on these simple facts, it was envisioned that 1-methoxy-3-trimethylsiloxy-1, 3-butadiene (Danishefsky's diene)[94] **181** would serve as the appropriate diene component in reactions with α,β-dehydrolactones **126** and **174** (Scheme 48). Thus addition of diene **181** to **126**

Scheme 48



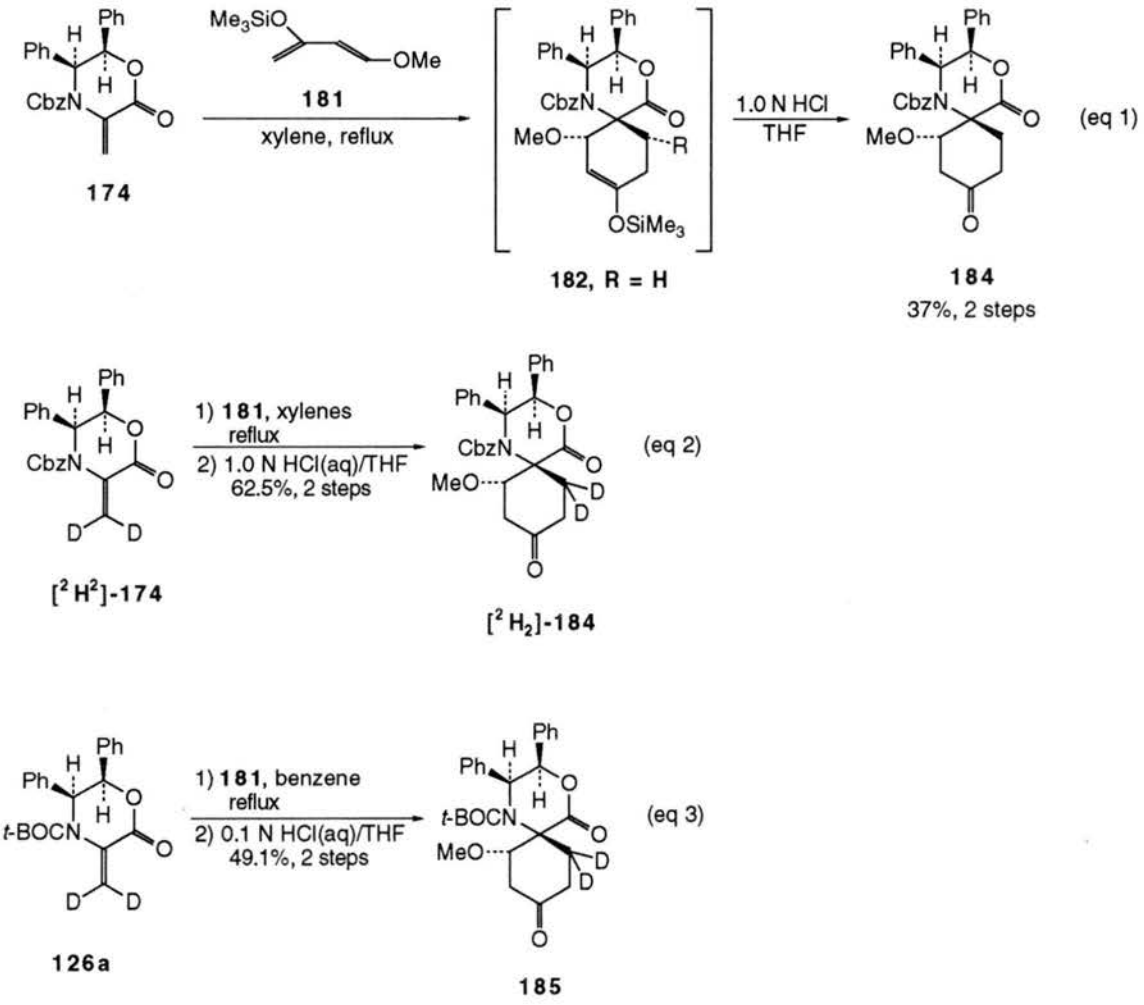


endo transition state

and **174** should be predicted to occur from the less hindered face of the carbon-carbon double bond, *anti* to the two phenyl substituents, to afford cycloadducts **182**. It was unclear whether the cycloaddition would occur via the endo transition state (i.e. the lactone carbonyl oriented endo to the approaching diene) or via that of the exo transition state. One could argue strongly in favor of the "endo" mode (shown in Scheme 48), especially in those cases where α,β-dehydrolactones **126** (R' = *t*-BOC) are used; the bulky *t*-BOC group would be expected to occupy a region of space required for diene approach via an exo transition state.

Regardless of the stereochemical outcome of the [4π + 2π] cycloaddition, it was anticipated that cycloadduct **182** could be hydrolyzed directly to spiro-fused cyclohexenone **183**, a potentially valuable synthon for highly functionalized amino acids (e.g. stereoselective cuprate 1,4-additions or carbonyl reductions followed by asymmetric epoxidations). The preliminary results of the Diels-Alder cycloadditions of diene **181** to α,β-dehydrolactones **126a** and **174** are illustrated in Scheme 49. Reaction of α,β-dehydrolactone **174** with diene **181** in refluxing xylenes provided cycloadduct **182** which was moderately unstable to flash silica chromatography (equation 1, Scheme 49).

Scheme 49



^{1}H NMR analysis of both the crude and partially purified cycloadduct strongly indicated that a single diastereomer of unknown relative and absolute stereochemistry was obtained! Treatment of **182** with 1.0 N HCl(aq)/THF mixture provided β-methoxyketone **184** in 37.1% yield for two steps. The yield for this reaction is low due to the extensive chromatography employed in this experiment. To simplify the ^{1}H NMR analysis of the reaction, deuterium-labelled **174** was also treated with diene **181** (equation 2, Scheme 49). After minimal flash silica chromatography and acidic hydrolysis of the initial cycloadduct, **[^{2}H$_2$]-184** was isolated as single diastereomer in approximately 63% overall yield. Again, no spiro-fused cyclohexenone adducts **183** were isolated. In subsequent experiments employing harsher hydrolysis conditions (stronger concentrations of HCl), the desired cyclohexenone products were detected by ^{1}H NMR.

Lastly, when α,β-dehydrolactone **126a** was treated with diene **181** and the corresponding cycloadduct hydrolyzed, β-methoxycyclohexenone **185** was isolated as a white crystalline solid in 49.1% yield (equation 3, Scheme 49). Complete analytical data (except x-ray crystallographic analysis) was obtained for this compound and is consistent with the structure shown in Scheme 49. Because of time constraints placed on the investigator, the relative and absolute stereochemistry of the cycloadducts (Scheme 49) were not determined. It is probable that this information can be obtained from specialized ^{1}H NMR techniques (e.g. nOe) or from x-ray crystallographic analysis, provided a suitable crystal can be produced. Nevertheless, a much more thorough study of Diels-Alder cycloadditions of various dienes to α,β-dehydrolactones must be undertaken to gain a better understanding of the scope and limitations of this methodology and to harness the full potential that it may offer.

References:

1) a) Burroughs, L. F. *Nature* **1957**, *179*, 360. b) Vähätalo, M-L.; Virtanen, A. I. *Acta Chem. Scand.* **1957**, *11*, 741. c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *121*, 1177.

2) Sakamura, S.; Ichihara, A.; Shiraishi, K.; Sato, H.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.

3) Mitchell, R. E. *Phytochemistry* **1985**, *24*, 1485.

4) a) Shiba, T.; Wakamiya, T.; Nakamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4411. b) Shiba, T.; Wakamiya, T.; Oda, Y.; Fujita, H. *Tetrahedron Lett.* **1986**, *27*, 2143.

5) a) Rance, M. J.; Ruddock, J. C.; Pacey, M. S.; Cullen, W. P.; Huang, L. H.; Jefferson, M. T.; Whipple, E. B.; Maeda, H.; Tone, J. *J. Antibiot.* **1989**, *42*, 206. b) Fox, K. R. *J. Antibiot.* **1990**, *43*, 1307. The name *Streptomyces braegensis* subsp. *japonicus* was proposed for the new actinomycete strain, N617-29, for which the UK-63,052 complex was isolated.

6) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231.

7) a) Adams, D. O.; Yang, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 170. b) Lurssen, K.; Naumann, K.; Schroder, R. Z. *Pflanzenphysiol.* **1979**, *92*, 285. c) Konze, J. R.; Kende, H. *Planta* **1979**, *146*, 293.

8) Abeles, F. B. Ethylene in Plant Biology 1973, Academic Press, New York.

9) a) Adams, D. O.; Yang, S. F. *Trends Biochem. Sci.* **1981**, *6*, 161. b) Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant Physiol.* **1982**, *70*, 195. c) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086. d) Adlington, R. M.; Baldwin, J. E.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 290. e) Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207. f) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48*, 5144. g) Peiser, G. D.; Wang, T-T.; Hoffman, N. E.; Yang, S. F.; Liu, H-W.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3059. h) Pirrung, M. C. *Bioorg. Chem.* **1985**, *13*, 219. i) Baldwin, J. E.;

Adlington, R. M.; Lajoie, G. A.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1496. j) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1044. k) Pirrung, M. C. *Biochemistry* **1986**, *25*, 114. l) Pirrung, M. C.; McGeehan, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 5647. m) Pirrung, M. C. *J. Org. Chem.* **1987**, *52*, 4179.

10) Honma, M.; Shimomura, T. *Agric. Biol. Chem.* **1978**, *42*, 1825.

11) Of the four possible diastereomers of coronamic acid (**2**), only the 1S,2S-isomer is processed by ACC Deaminase: Honma, M.; Shimomura, T.; Shiraishi, K.; Ichihara, A.; Sakamura, S. *Agric. Biol. Chem.* **1979**, *43*, 1677.

12) a) Walsh, C. T.; Pascal, R. A., Jr.; Johnston, M.; Raines, R.; Dikshit, D.; Krantz, A.; Honma, M. *Biochemistry*, **1981**, *20*, 7509. b) Hill, R. K.; Prakash, S. R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Walsh, C. T.; Liu, H-W. *J. Am. Chem. Soc.* **1984**, *106*, 795. c) Liu, H-W.; Auchus, R.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 5335.

13) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Series Ed.; Organic Chemistry Series; Pergamon Press: Oxford, 1989.

14) a) Schöllkopf, U.; Harms, R.; Hoppe, D. *Justus Liebigs Ann. Chem.* **1973**, 611. b) Ichihara, A.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, 269. c) O'Donnell, M. J.; Bruder, W. A.; Eckrich, T. M.; Shullenberger, D. F.; Staten, G. S. *Synthesis* **1984**, 127. d) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J. *Tetrahedron Lett.* **1985**, *26*, 481. e) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1044. f) Logusch, E. W. *Tetrahedron Lett.* **1986**, *27*, 5935. g) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103. h) Subramanian, P. K.; Woodard, R. W. *J. Org. Chem.* **1987**, *52*, 15. i) Marco, J. L. *Heterocycles* **1987**, *26*, 2579. j) Aitken, D. J.; Royer, J.; Husson, H-P. *Tetrahedron Lett.* **1988**, *29*, 3315. k) Subramanian, P. K.; Kalvin, D. M.; Ramalingam, K.; Woodard, R. W. *J. Org. Chem.* **1989**, *54*, 270. l) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. m) Aitken, D. J.; Royer, J.; Husson, H-P. *J. Org. Chem.* **1990**, *55*, 2814. This category includes the stereoselective Hofmann degradation or Curtius rearrangement of cyclopropane-1,1-dicarboxylates.

15) a) Bregovec, I.; Jakovcic, T. *Monatsh. Chem.* **1972**, *103*, 288. b) Hines, J. W., Jr.; Breitholle, E. G.; Sato, M.; Stammer, C. H. *J. Org. Chem.* **1976**, *41*, 1466. c) Shiraishi,

K.; Ichihara, A.; Sakamura, S. *Agric. Biol. Chem.* **1977**, *41*, 2497. d) Hiyama, T.; Kai, M. *Tetrahedron Lett.* **1982**, *23*, 2103. e) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270. f) Kimura, H.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 2440. g) Suzuki, M.; Kumar, S. D.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 4769. h) Suzuki, M.; Gooch, E. E.; Stammer, C. H. *Tetrahedron Lett.* **1983**, *24*, 3839. i) Arenal, I.; Bernabé, M.; Fernández-Alvarez, E.; Izquierdo, M. L.; Penadés, S. *J. Heterocyclic Chem.* **1983**, *20*, 607. j) Izquierdo, M. L.; Arenal, I.; Bernabé, M.; Fernández-Alvarez , E. *Tetrahedron* **1985**, *41*, 215. k) Arenal, I.; Bernabé, M.; Fernández-Alvarez, E.; Penadés, S. *Synthesis* **1985**, 773. l) Bland, J.; Shah, A.; Bortolussi, A.; Stammer, C. H. *J. Org. Chem.* **1988**, *53*, 992. m) Elrod, L. F.; Holt, E. M.; Mapelli, C.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1988**, 252. n) Mapelli, C.; Turocy, G.; Switzer, F. L.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 145. o) Lalitha, K.; Iyengar, D. S.; Bhalerao, U. T.*J. Org. Chem.* **1989**, *54*, 1771. p) Srivastava, V. P.; Roberts, M.; Holmes, T.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 5866. q) Fernández, D.; de Frutos, P.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1989**, *30*, 3101. r) Slama, J. T.; Satsangi, R. V.; Simmons, A.; Lynch, V.; Bolger, R. E.; Suttie, J. *J. Med. Chem.* **1990**, *33*, 824. s) Alami, A.; Calmes, M.; Daunis, J.; Escale, F.; Jacquier, R.; Roumestant, M-L.; Viallefont, P. *Tetrahedron: Asymmetry* **1991**, *2*, 175. t) Alcaraz, C.; Herrero, A.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1992**, *33*, 5605.

16) *Chem. Abst.* **1973**, *78*, 3793g; Hayman, D. F. *Ger. Offen.* **1973**, 2201514.

17) Schöllkopf, U.; Hupfeld, B.; Gull, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 754.

18) a) DeKimpe, N.; Sulmon, P.; Verhe, R.; DeBuyck, L.; Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320. b) DeKimpe, N.; Sulmon, P.; Brunet, P.; Lambein, F.; Schamp, N. *Tetrahedron Lett.* **1989**, *30*, 1863. c) DeKimpe, N.; Sulmon, P.; Schamp, N. *Tetrahedron Lett.* **1989**, *30*, 5029. d) DeKimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777.

19) a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

20) von der Muhll, P. A.; Settimj, G.; Arigoni, D. *Chimia* **1965**, *19*, 595.

21) Bose, A. K.; Manhas, M. S.; Tavares, R. F.; van der Veen, J. M.; Fujiwara, H. *Heterocycles* **1977**, *7*, 1227.

22) Schöllkopf, U.; Nozulak, J.; Groth, U. *Tetrahedron* **1984**, *40*, 1409.

23) (R)-(+)-2-methyl-3-phenylalanine, methyl ester (**31**) was obtained via an asymmetric Strecker synthesis from phenylacetone (64% yield, 4 steps, > 98% ee). See, Subramanian, P. K.; Woodard, R. W. *Synth. Commun.* **1986**, *16*, 337.

24) a) Wang, S. S.; Tam, J. P.; Wang, B. S. H.; Merrifield, R. B. *Int. J. Peptide Protein Res.* **1981**, *18*, 459. b) Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, *33*, 864.

25) In this case syn refers to alkylation occurring on the same face of the bis(lactim ether) **34** as the larger benzyl group.

26) Scott, J. W.; Keith, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086.

27) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.

28) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.

29) Schöllkopf, U.; Hupfeld, B.; Küper, S.; Egert, E.; Dyrbusch, M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 433.

30) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798.

31) Carbene intermediate **50** has been previously prepared: Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 192.

32) Marco, J. L.; Royer, J.; Husson, H-P. *Tetrahedron Lett.* **1985**, *26*, 3567.

33) Aitken, D. J.; Guillaume, D.; Husson, H-P. *Tetrahedron* **1993**, *49*, 6375.

34) a) Miller, A. E.; Bischoff, J. J. *Synthesis* **1986**, 777. b) Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. M.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882. c) Kim, K.; Lin, Y-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183.

35) Baltazzi, E.; Robinson, R. *Chem. Ind.* **1954**, 191.

36) Poisel, H.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 3408.

37) (1R,2R,5R)-(+)-2-hydroxy-3-pinanone (**85**) can be prepared from the $KMnO_4$ oxidation of commercially inexpensive (1R)-(+)-α-pinene using the procedure of Schmidt, H. *Chem. Ber.* **1960**, *93*, 2485.

38) Amarego, W.; Milloy, B.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229.

39) Dale, J.; Dull, J.; Mosher, H. *J. Org. Chem.* **1969**, *34*, 2543.

40) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.

41) Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245.

42) (S)-epichlorohydrin (**98**) was prepared from commercially available (R)-oxirane-2-methyl tosylate, analogous to the procedure of reference 51.

43) Gaucher, A.; Ollivier, J.; Salaün, J. *Synlett* **1991**, 151.

44) a) Keirs, D.; Overton, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1660. b) Dufour, M.; Gramain, J. C.; Husson, H-P.; Sinibaldi, M. E.; Troin, Y. *Tetrahedron Lett.* **1989**, *30*, 3429. c) Dufour, M.; Gramain, J. C.; Husson, H-P.; Sinibaldi, M. E.; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483.

45) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. H. *Tetrahedron Lett.* **1985**, *26*, 485.

46) a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. b) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021. c) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482. d) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. e) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. f) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723. g) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425. h) Williams, R. M.; Aldous, D. J.; Aldous, S. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 171. i) Williams, R. M.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1990**, *55*, 4657. j) Williams, R. M.; Im, M-N. *Tetrahedron Lett* **1988**, *29*, 6075. k) Williams, R. M.; Im, M-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. l) Williams, R. M.; Im, M-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976. m) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Syn Lett.* **1992**, 249.
For a comprehensive review of this work, see: n) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11.

47) Both antipodes of the *t*-BOC- and Cbz-protected oxazinones **112/113** are commercially available from Aldrich Chemical Company, Inc.: **112a**, Cat. No. 33,184-8; **112b**, Cat No. 33,181-3; **113a**, Cat. No. 33,187-2; **113b**, Cat. No. 33,185-6.

48) Vigneron, J. P.; Kagan, H.; Horeau, A. *Tetrahedron Lett.* **1968**, 5681.

49) a) Weijlard, J.; Pfister, K.; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216. b) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021. c) Lohray, B. B.; Ahuja, J. R. *J. Chem. Soc., Chem. Commun.* **1991**, 95.

50) Both *erythro*-**120a** and **120b** are commercially available from Aldrich Chemical Company, Inc.: **120a**, Cat. No. 33,,189-9; **120b**, Cat. No. 33,188-0.

51) *t*-BOC-protected oxazinones **112a/b** were chosen over the Cbz-protected oxazinones **113a/b** because of deprotection considerations discussed earlier. Cyclopropane derivatives of **113a/b** were not expected to withstand the hydrogenation conditions (Scheme 26, Method D) used in obtaining the free amino acids directly.

52) α-Phosphorylglycine derivatives are well precedented. For leading references, see: a) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645. b) *idem.ibid.*, **1973**, 4649. c) Edwards, J. A.; Kluge, A. F.; Scopes, D. I. C. *J. Org. Chem.* **1977**, *42*, 376. d)

Schollkopf, U.; Rachon, J. *Liebigs Ann. Chem.* **1981**, 1693. e) Schmidt, U.; Lieberknecht, A.; Schanbacher, U.; Beuttler, T.; Wild, J. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 776. f) Schmidt, U.; Lieberknecht, A.; Schanbacher, U.; Beuttler, T.; Wild, J. *Angew. Chem. Suppl.* **1982**, 1682. g) Steglich, W.; Kober, R. *Liebigs Ann. Chem.* **1983**, 599. h) Schmidt, U.; Beuttler T.; Lieberknecht, A.; Griesser, H. *Tetrahedron Lett.* **1983**, *24*, 3573. i) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53. j) Schmidt, U.; Wild, J. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 991. k) Schmidt, U.; Wild, J. *Liebigs Ann. Chem.* **1985**, 1882. l) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159. m) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227. n) Seebach, D.; Schickli, C. P. *Liebigs Ann.* **1991**, 655.

53) The availability CCl_4 from commercial suppliers has essentially ceased due to strict new environmental regulations enforced by the U. S. government. A suitable replacement for this solvent will be necessary for future bromination reactions.

54) It is assumed that the aldehyde approaches only from the less hindered face of the oxazinone ring eliminating the other two diastereomeric transition states (see Reno, D.S.; Lotz, B.T.; Miller, M.J., *Tetrahedron Lett.* **1990**, *31*, 827.).

55) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

56) Only one set of cyclopropyl methylene doublets appeared in $CDCl_3$.

57) a) Ref. 12b. b) Ref. 14h. In two previous synthesis of [$^2H_2$]-ACC, ^1H NMR was used as a direct and indirect means of assessing the %ee of the product amino acid. In the Woodard synthesis, a direct assessment of the enantiomeric excess was obtained from the corresponding deuterated cyclopropyl-containing Schollkopf bis(lactim ether). The Arigoni synthesis utilized the diketopiperazine, cyclo[(S)-Phe-[$^2H_2$]ACC], as the method to assign %ee.

58) Trozzolo, A. M.; Murray, R. W. *J. Am. Chem. Soc.* **1961**, *26*, 3109.

59) a) Johnson, C. R.; Janiga, E. R.; Haake, M. *J. Am. Chem. Soc.* **1968**, *90*, 3890. b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6852. c) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. d) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. e) Johnson, C. R.; Schroeck, C. W.;

Shanklin, J. R. *J. Am. Chem. Soc.* **1973,** *95*, 7424. f) Johnson, C. R.; Janiga, E. R. *J. Am. Chem. Soc.* **1973,** *95*, 7692. g) Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1793. h) Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1798.

60) For a comprehensive review on the synthetic applications of sulfoximines, see: Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3.

61) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. H. *Tetrahedron Lett.* **1985**, *26*, 485.

62) The details of all x-ray crystal structure determinations will be published elsewhere.

63) Stammer, C. H.; Kimura, H. *J. Org. Chem.* **1983**, *48*, 2440.

64) Mapelli, C.; Kimura, H.; Stammer, C. H. *Int. J. Peptide Protein Res.* **1986**, 347.

65) Ellman, J. A.; Mendel, D.; Schultz, P. G. *Science*, **1992**, *255*, 197.

66) Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Rake, J. B. *J. Med. Chem.* **1988**, *31*, 1694.

67) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

68) Note that while the Cahn-Ingold-Prelog stereochemical assignment has changed for this amino acid, the absolute stereochemistry relative to the previously discussed examples has not.

69) Wong, H. N. C.; Hon, M-Y.; Tse, C-W.; Yip, Y-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, 165.

70) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, 566.

71) a) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002. b) Inaba, T.; Kozono, I.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2359.

72) Williams, R. M.; Fegley, G. J. *J. Org. Chem.* **1993**, *58*, 0000.

73) Walborsky, H. M.; Ronman, P. E. *J. Org. Chem.* **1973**, *38*, 4231.

74) Attempts were made to isolate and subsequently saponify the amino acid methyl ester derived directly from the acid hydrolysis reaction of the crude imine. However, isolation of cyclopropylPhe **142** in this fashion failed, and thus supports work published by Stammer and coworkers (Reference 15e). Therefore, it is essential that the nitrogen atom be protected prior to ester saponification.

75) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

76) For a racemic synthesis of E- and Z-cyclopropyltyrosine **37**, see: a) Mapelli, C.; Turocy, G.; Switzer, F. L.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 145. b) Suzuki, M.; Orr, F. G.; Stammer, C. H. *Bioorg. Chem.* **1987**, *15*, 43.

77) A racemic synthesis of cyclopropylDOPA **38** has been documented. See: a) Smith Kline & French Laboratories (by Kaiser, C.; Zirkle, C. L.) Belgium Patent 648,020; Nov. 16, 1964. b) Chem. Abstr. **1965**, *63*, 14979b.

78) Loew, G. H.; Burt, S. K. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 7.

79) Wiseman, J. S.; Nichols, J. S. *J. Biol. Chem.* **1984**, *259*, 8907.

80) Antia, M.; Hoare, D. S.; Work, E. *Biochem. J.* **1957**, *65*, 448.

81) a) Fischer, L. M.; Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2538. b) Fisher, L. M.; Belasco, J. G.; Bruice, T. W.; Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2543. c) Belasco, J. G.; Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2552. d) Belasco, J. G.; Bruice, T. W.; Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2558. e) Belasco, J. G.; Bruice, T. W.; Fisher, L. M.; Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2564. f) Albery, W. J.; Knowles, J. R. *Biochemistry* **1986**, *25*, 2572.

82) Compounds **157** - **161** are the most potent DAP epimerase inhibitors known to date: a) Baumann, R. J.; Bohme, E. H.; Wiseman, J. S.; Vaal, M.; Nichols, J. S. *Antimicrob.*

Agents Chemother. **1988**, *32*, 1119. b) Lam, L. K. P.; Arnold, L. D.; Kalantar, T. H.; Kelland, J. G.; Lane-Bell, P. M.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1988**, *263*, 11814. c) Gerhart, F.; Higgins, W.; Tardif, C.; Ducep, J-B. *J. Med. Chem.* **1990**, *112*, 4932. d) Gelb, M. H.; Lin, Y.; Pickard, M. A.; Song, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4932.

83) There is some precedence for ring opening of activated cyclopropanes by thiolate nucleophiles. See: a) Kondo, K.; Umemoto, T.; Takahatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977**, 113. b) Zutterman, E.; DeWilde, H.; Mingheer, R.; De Clercq, P.; Vandevalle, H. *Tetrahedron Lett.* **1979**, *35*, 2389. c) Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940. d) Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1979**, *101*, 6076. d) Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 941. For an enzyme-mediated nucleophilic opening of an activated cyclopropane, see reference 12.

84) Shoji, J.; Hinoo, H.; Kato, T.; Nakauchi, K.; Matsuura, S.; Mayama, M.; Yasuda, Y.; Kawamura, Y. *J. Antibiot.* **1981**, *34*, 374.

85) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519.

86) A comparison of the ^{1}H NMR spectra of **170** and cyclopropyllactone **126c**[67] provides convincing evidence for the assigned stereochemistry.

87) Fang, S.; Li, L.; Niu, C.; Tseng, K. *Sci. Sinica* **1961**, *10*, 845.

88) Fan, H.; Lin, C. *Wu Li Hsueh Pao* **1965**, *21*, 253.

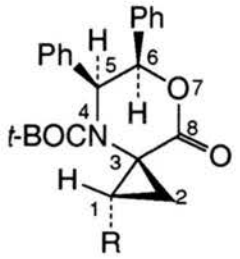
89) a) Monteiro, H. J. *J. Chem. Soc., Chem. Comm.*. **1973**, 2. b) Sun, T.; Loh, S.; Chow, S.; Kyi, Z. *Sci. Sinica* **1961**, *10*, 852.

90) Achiwa, K.; Morimoto, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3845.

91) a) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762. b) Imai, N.; Terao, Y.; Achiwa, K. *Yuki Gosei Kagaku Kyokai Shi* **1985**, *43*, 862. c) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235.

92) Williams, R. M.; Fegley, G. J. *Tetrahedron Lett.* **1992**, *113*, 6755.

93) The numbering system for the spiro-fused cyclopropyl lactones is shown below:



94) a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. b) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth., Coll.Vol. 9*, **1990**, 312.

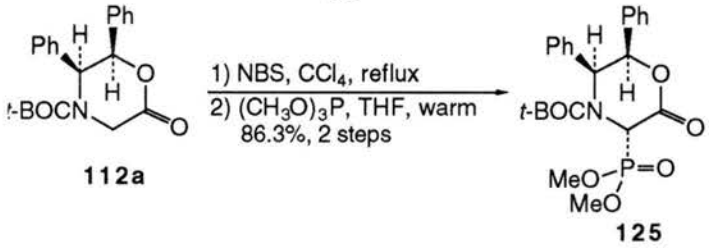
Chapter Three

Experimental Section

3.1 Experimental Procedures and Data

General Information

^1H NMR spectra were obtained on a Bruker AC 300 MHz spectrometer and chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR and are reported as λmax in cm^{-1}. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at a wavelength of 589 nm (sodium "D" line) with a 1.0-dm cell with a 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. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within $\pm$ 0.4% of the calculated values. High resolution mass spectra were performed by the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE, (partially supported by the NSF, Biology Division (Grant No. DIR9017262)) and are accurate to within $\pm$ 3 millimass units. Column chromatography was performed with Merck silica gel grade 60, 230-400 mesh, 60 Å. Reagents and solvents were dried or purified in the following way: Tetrahydrofuran and benzene were each distilled from sodium benzophenone ketyl. Carbon tetrachloride, dichloromethane, dimethyl sulfoxide, diisopropylamine, ethanol, and triethylamine were each distilled from CaH_2. Methanol and trimethylphosphite were distilled from Na°. Acetaldehyde, propionaldehyde, butyraldehyde, benzaldehyde, isobutyraldehyde, and *p*-anisaldehyde were dried over $CaCl_2$ and freshly distilled prior to use. Anhydrous ammonia was distilled from lithium metal. HMPA was dried over 4Å molecular sieves. N-bromosuccinimide was recrystallized from H_2O and dried under high vacuum prior to use. Lead tetraacetate was recrystallized from glacial acetic acid and stored under Argon at 0 °C. All other reagents were used in commercial grade form. Purification of the free amino acids was accomplished by one or both of two methods: elution of an aqueous sample with H_2O on a Sep-Pak® C_{18} (reverse phase) cartridge manufactured by Waters, a Division of Millipore Corporation; or elution of the hydrochloride salt with 0.5 - 1.0 N NH_4OH on a column packed with Dowex® 50x8-100 cation-exchange resin.

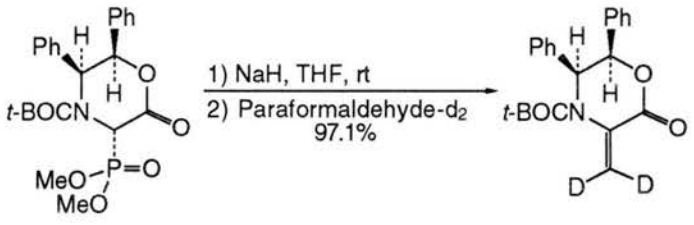


112a **125**

(3S,5S,6R)-4-(*tert*-butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (125).

To a flask containing **112a** (3.0 g, 8.49 mmol, 1.0 equiv) and NBS (1.7 g, 9.34 mmol, 1.1 equiv) was added CCl_4 (500 mL). The mixture was refluxed for 1h and then cooled to 0 °C, filtered through Celite to remove succinimide, and concentrated *in vacuo* to yield the bromide as a white solid. To the crude bromide was added THF (36 mL) and trimethylphosphite (1.1 mL, 9.34 mmol, 1.1 equiv) and the mixture was gently refluxed for 12h. The mixture was then cooled to room temperature and concentrated providing a yellow viscous oil. Purification via flash silica chromatography (160 g silica, eluted with 1:10-1:1 EtOH/Hexanes) provided 3.4 g (86.3%, two steps) of **125** as a white crystalline solid:

^{1}H NMR (300 MHz)(DMSO-d_6)δTMS: 1.03(s) and 1.39(s)(9H), 3.81-3.93(6H, m), 5.25(d, J = 3.1 Hz) and 5.33(d, J = 2.9 Hz)(1H), 5.54-5.68(1H, m), 6.18(d, J = 2.9 Hz) and 6.33(d, J = 3.1 Hz)(1H), 6.55-6.59(2H, m), 7.04-7.31(8H, m); IR(KBr)υ: 3030, 3019, 2976, 2964.7, 2921, 2856, 1959, 1889, 1747, 1703, 1295, 1273, 1049, 1028 cm^{-1}; $[\alpha]_D^{25}$ = -38.55 ° (c = 1.0, CH_2Cl_2); mp = 143-144 °C.Anal.(recrystallized from EtOH) Calcd for $C_{23}H_{28}NO_7P$: C, 59.87; H, 6.12; N, 3.04. Found: C, 59.82; H, 6.21; N, 3.10.



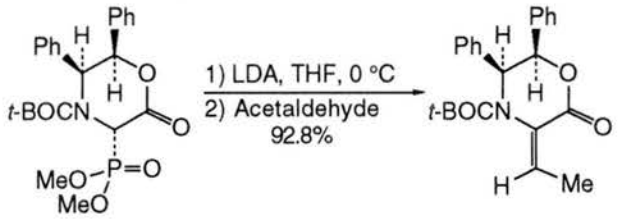
125 **126a**

(5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-([$^2H_2$]methylidene)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126a).

To a flask containing **125** (619.7 mg, 1.34 mmol, 1.0 equiv) and 50% NaH dispersion (64.5 mg, 1.34 mmol, 1.0 equiv) was added THF (15 mL) at room temperature. The resulting solution was stirred for 1 h, and then paraformaldehyde-d_2 (43.0 mg, 1.34 mmol, 1.0 equiv) was added in one portion. After stirring the reaction for 24 h, sat'd NH_4Cl was added, followed by extraction with 3 x 5 mL EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (20 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) provided 479 mg (97.1%) **126a** as a white crystalline solid:

^1H NMR(300 MHz)($CDCl_3$)δTMS: 1.27(9H, s), 5.29(1H, d, J = 2.8 Hz), 5.79(1H, d, J = 2.8 Hz), 6.65-6.68(2H, m), 7.00-7.32(8H, m); IR(KBr)υ: 3090, 3065, 3034, 3004, 2985, 2932, 1954, 1889, 1736, 1705, 1570, 1560, 1455, 1387, 1353, 1297, 1282, 1269, 1154, 1066 cm^{-1}; $[\alpha]_D^{25}$ = -111.3 ° (c = 1.0, CH_2Cl_2); mp = 163-165 °C.

Anal.(recrystallized from EtOH) Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.54; H, 6.45; N, 3.86. A single crystal x-ray analysis of this compound has been solved (Figure 10).[67]



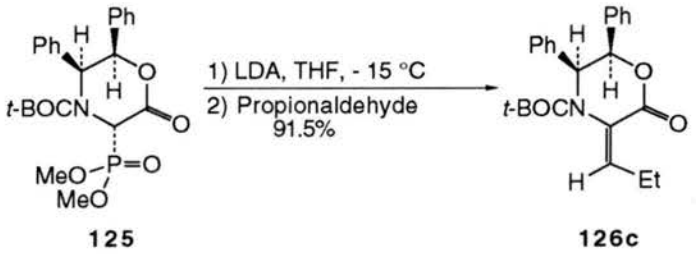
125 **126b**

(E)-(5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-ethylidene-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126b).

To a 0 °C solution of **125** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (5 mL) was added 0.5 M LDA in THF (4.35 mL, 2.17 mmol, 1.0 equiv) via cannula. After stirring this mixture for 1 h, acetaldehyde (606 mL, 10.84 mmol, 5.0 equiv) was added rapidly via syringe and the resulting mixture was stirred for 7 h at 0 °C and an additional 12 h at room temperature. The reaction was quenched with 3 mL brine and extracted with 3 x 5 mL EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated.

Purification via flash silica chromatography (50 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) provided 763.3 mg (92.8%) **126b** as a white crystalline solid:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.14(9H, s), 2.17(3H, d, J = 7.5 Hz), 5.16(1H, d, J = 1.9 Hz), 5.72(1H, d, J = 2.8 Hz), 6.66-6.83(3H, m), 6.96-6.99(2H, m), 7.07-7.28(6H, m); IR(KBr)υ: 3065, 3027, 3016, 2989, 2974, 2929, 2918, 1749, 1713, 1637, 1630, 1458, 1378, 1371, 1353, 1333, 1280, 1259, 1233, 1152, 1061 cm^{-1}; $[\alpha]_D^{25}$ = -123.3 ° (c = 1.0, CH_2Cl_2); mp = 168-170 °C; Anal.(recrystallized from EtOH). Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.77; H, 6.82; N, 3.73. A single crystal x-ray analysis of this compound has been solved (Figure 5).[67]



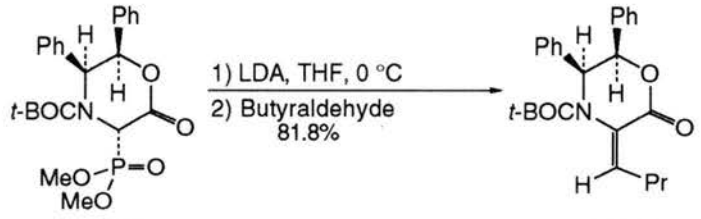
125 **126c**

(E)-(5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-propylidene-2,3,5,6-tetrahydro-1,4-oxazin-2-one (126c).

To a -15 °C solution (ice/MeOH) of **125** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (2 mL) was added 3.7 mL 0.6 M LDA in THF (2.17 mmol, 1.0 equiv) via syringe. The resulting reaction was stirred for 1.5 hr, followed by addition of propionaldehyde (1.6 mL, 21.67 mmol, 10.0 equiv) at -15 °C. The reaction was slowly warmed to room temperature and was stirred for 20 hrs, followed by quenching with 5 mL saturated NaCl and extraction with 3 x 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash silica gel chromatography (68 g silica, eluted with 1:1 EtOAc/Hexanes) provided 780 mg (91.5%) of **126c** as a white crystalline solid:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.14-1.19(12H, m), 2.51-2.74(2H, m), 5.16(1H, d, J = 1.95 Hz), 5.72(1H, d, J = 2.89 Hz), 6.63-6.70(3H, m), 6.96-6.99(2H, m), 7.07-7.28(6H, m); IR(NaCl, neat)υ: 3089, 3067, 3033, 2978, 2933, 2878, 1739, 1711, 1628, 1283.3, 1233, 1161 cm^{-1}; $[\alpha]_D^{25}$ = -135.3 ° (c = 1.0, CH_2Cl_2); mp = 158.5-160 °C; Anal.

(recrystallized from EtOH) Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.06; H, 7.03; N, 3.65.

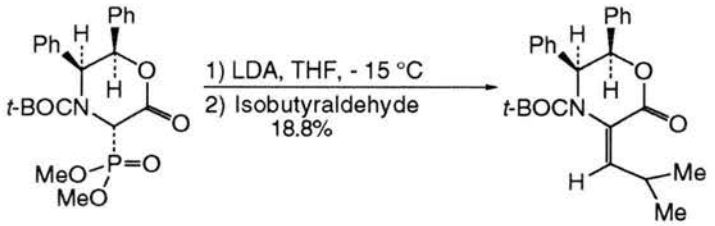


125 126d

(E)-(5S,6R)-4-(*tert*-butoxycarbonyl)-3-butylidene-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126d).

To a 0 °C solution of **125** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (4 mL) was added 0.5 M LDA in THF (4.3 mL, 2.17 mmoL, 1.0 equiv). The mixture was stirred for 1 h at 0 °C and then butyraldehyde (976.7 µL, 10.84 mmol, 5.0 equiv) was added via syringe, maintaining the temperature at 0 °C for 16 h and then stirring at room temperature for 2 days. To the mixture was added brine (3 mL), followed by extraction with 3 x 5 mL EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (45 g silica, eluted with 1:10 EtOAc/Hexanes) provided 722.5 mg (81.8%) **126d** as a white crystalline solid and 64.1 mg (6.4%) recovered starting material:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.01(3H, t, J = 7.4 Hz), 1.16(9H, s), 1.58(2H, m), 2.61(2H, m), 5.17(1H, apparent s), 5.71(1H, d, J = 2.9 Hz), 6.62-6.69(3H, m), 6.96-7.00(2H, m), 7.07-7.26(6H, m); IR(KBr)υ: 3090, 3067, 3032, 3002, 2965, 2931, 2871, 1734, 1708, 1637, 1630, 1454, 1387, 1287, 1259, 1227, 1164, 1123, 1058 cm^{-1}; $[\alpha]_D^{26}$ = -127.9 ° (c = 1.0, CH_2Cl_2); mp = 167-169 °C; Anal. (recrystallized from EtOH) Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.56; H, 7.18; N, N, 3.38.



125 126e

(E)-(5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-isobutylidene-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126e).

To a -15 °C solution of **125** (354.2 mg, 0.77 mmol, 1.0 equiv) in THF (1mL) was added 0.5 M LDA (1.6 mL, 0.77 mmol, 1.0 equiv) via cannula. After stirring for 15 min., isobutyraldehyde (697.1 μL, 7.68 mmol, 10.0 equiv) was added while maintaining a -15 °C temperature for 8.0 h. The reaction was then stirred for 30 h at room temperature, quenched with brine (3 mL), and extracted with 3 x 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, and filtered. Purification via flash silica chromatography (26 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) provided 168.7 mg of a co-eluting fraction and recovered starting material. The mixed fraction was recrystallized from EtOH to provide 72.1 mg (23.1%) **126e** as a white crystalline solid:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.07(3H, d, J = 6.6 Hz), 1.18(9H, s), 1.27(3H, d, J = 6.6 Hz), 3.21-3.33(1H, m), 5.16(1H, apparent s), 5.71(1H, d, J = 2.9 Hz), 6.42(1H, m), 6.67-6.70(2H, m), 6.96-7.32(8H, m); IR(KBr)υ: 3089, 3065, 3028, 3005, 2972, 2927, 2869, 1734, 1714, 1629, 1456, 1388, 1350, 1295, 1283, 1259, 1238, 1160, 1126, 1056 cm^{-1}; $[\alpha]^{25}_D$ = -127.8 ° (c = 1.0, CH_2Cl_2); mp = 197-198.5 °C; Anal.(recrystallized from EtOH) Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.56; H, 7.18; N, 3.38.

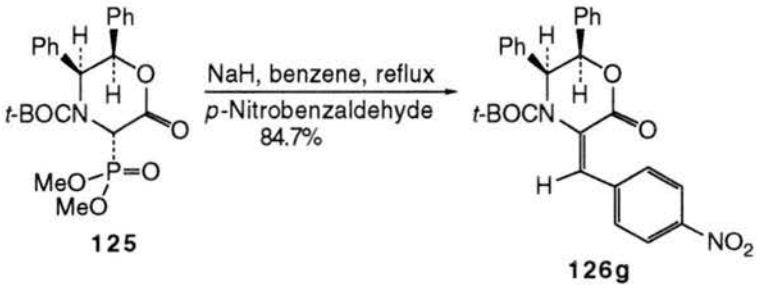
125 **126f**

(E)-(5S,6R)-3-benzylidene-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126f).

To a flask containing **125** (1.0 g, 2.17 mmol, 1.0 equiv) and 50% NaH dispersion in oil (104 mg, 2.17 mmol, 1.0 equiv) was added benzene (15 mL). The reaction was stirred 6.5 h at room temperature, followed by addition of benzaldehyde (242.3 μL, 2.38 mmol, 1.1 equiv) via syringe. The flask was fitted with a Dean-Stark trap and condenser and the reaction was heated such that benzene could distill off at a slow rate. The reaction

was concentrated to ~1 mL volume, heated gently overnight, cooled to room temperature, and purified via flash silica chromatography (30 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) to provide 922.8 mg (96.4%) of **126f** as a white crystalline solid and ~4% recovered starting material:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.20(9H,s), 5.25(1H, d, J = 2.7 Hz), 5.89(1H, d, J = 2.7 Hz), 6.70-6.73(2H, m), 6.99-7.57(14H, m); IR(KBr)υ: 3096, 3063, 3030, 2997, 2976, 2932, 1960, 1905, 1741, 1703, 1627, 1605, 1453, 1344, 1305, 1235, 1213, 1158 cm^{-1}; $[\alpha]_D^{25}$ = - 141.8 ° (c = 1.0, CH_2Cl_2); mp = 187-189 °C; Anal.(recrystallized from EtOH) Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.16; H, 6.12; N, 3.14. A single crystal x-ray analysis of this compound has been solved (Figure 6).[67]

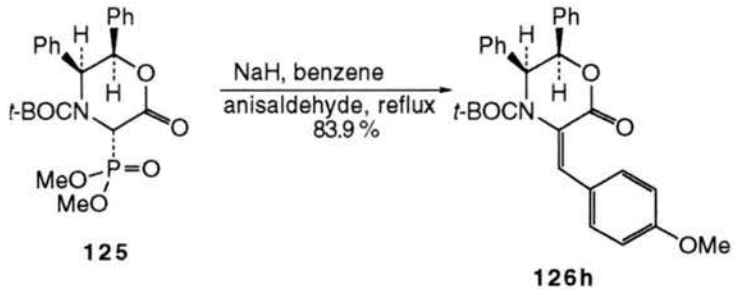


(E)-(5S,6R)-5,6-diphenyl-3-(4'-nitrobenzylidene)-4-(*tert*-butoxycarbonyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126g).

To a mixture of **125** (200 mg, 0.43 mmol, 1.0 equiv) and degreased NaH (10.4 mg, 0.43 mmol, 1.0 equiv) was added benzene (10 mL). The resulting slurry was stirred for 1h, followed by additon of 4-nitrobenzaldehyde (72.0 mg, 0.48 mmol, 1.1 equiv). After stirring this mixture for 0.5 h, the flask was fitted with a Dean-Stark trap and condenser and the reaction was heated such that benzene could be distilled of at a slow rate. The reaction was concentrated to ~ 1mL volume, heated gently for 5h, and then cooled to room temperature. The crude residue was redissolved in CH_2Cl_2 (8 mL), washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (11.2 g silica, eluted with 1:10 EtOAc/Hexanes) provided 178.5 mg (84.7%) of **126g** as a light yellow crystalline solid:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.20(9H, s), 5.27(1H, d, J = 2.7 Hz), 5.90(1H, d, J = 2.7 Hz), 6.70(2H, apparent d, J = 7.3 Hz), 6.99-7.02(2H, m), 7.11-7.33(6H, m),

7.69(3H, apparent d, J = 9.1 Hz), 8.21(2H, d, J = 8.8 Hz); IR(KBr)υ: 3067, 3034, 2977, 2934, 1750, 1709, 1599, 1519, 1346, 1284, 1258, 1209, 1155, 1059 cm^{-1}; $[\alpha]^{25}_D$ = -150.1° (c = 1.02, CH_2Cl_2); mp = 203-204 °C; Anal.(recrystallized from EtOH) Calcd for $C_{28}H_{26}N_2O_6$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.95; H, 5.44; N, 5.73.

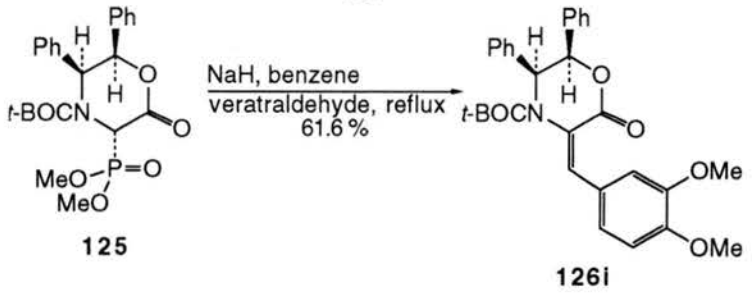


125 126h

(E)-(5S,6R)-5,6-diphenyl-3-(4'-methoxybenzylidene)-4-(*tert*-butoxycarbonyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126h).

To a room temperature mixture of **125** (300.0 mg, 0.65 mmol, 1.0 equiv) and degreased NaH (15.6 mg, 0.65 mmol, 1.0 equiv) was added benzene (10 mL). After stirring the mixture for 0.5 h, *p*-anisaldehyde (791.0 mL, 6.50 mmol, 10.0 equiv) was added and immediately the grey slurry turned to a light yellow clear solution. The benzene was slowly and completely distilled via a Dean-Stark apparatus and the reaction mixture was kept warm overnight. After cooling the reaction to room temperature, CH_2Cl_2 (10 mL) was added to the crude residue and washed with H_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. Purification via flash silica chromatography (18 g silica, 1:10 - 1:1 EtOAc/hexanes) provided 257.3 mg (83.9%) **126h** as a light yellow solid.

^1H NMR(300 MHz)($CDCl_3$)δTMS: 1.18(9H, s), 3.83(3H, s), 5.23(1H, d, J = 2.5 Hz), 5.86(1H, d, J = 2.8 Hz), 6.71-6.73(2H, m), 6.86-6.91(2H, m), 6.98-7.01(2H, m), 7.09-7.29(6H, m), 7.43(1H, broad s), 7.56-7.60(2H, m); IR(KBr)υ: 3103, 3065, 3031, 3005, 2974, 2932, 1737, 1702, 1605, 1512, 1303, 1265, 1238, 1155, 1025 cm^{-1}; $[\alpha]_D^{25}$ = - 143.7 ° (c = 1.0, CH_2Cl_2); mp = 193-195 °C. Anal.(recrystallized from EtOH). Calcd for $C_{29}H_{29}NO_5$: C, 73.87; H, 6.20; N, 2.97. Found: C, 73.80; H, 6.30; N, 2.97.

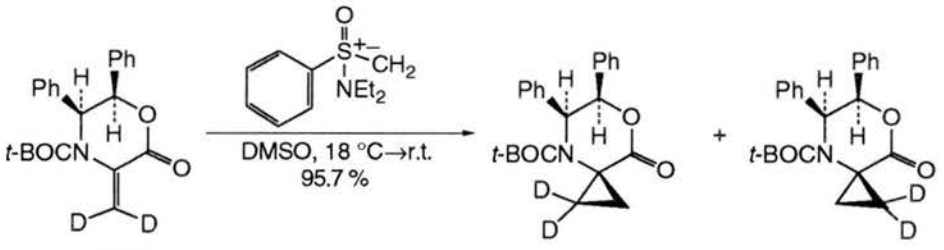


125 126i

(E)-(5S,6R)-5,6-diphenyl-3-(3',4'-dimethoxybenzylidene)-4-(*tert*-butoxycarbonyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (126i).

A mixture of **125** (500.0 mg, 1.08 mmol, 1.0 equiv), degreased NaH (28.6 mg, 1.19 mmol, 1.1 equiv), veratraldehyde (900.3 mg, 5.42 mmol, 5.0 equiv), and benzene (10 mL) was heated to reflux and the solvent was removed slowly and completely via a Dean Stark apparatus. The reaction was kept warm and stirred overnight. After this time the reaction was cooled to room temperature, dissolved in EtOAc (10 mL), and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography (1:5 EtOAc/hexanes) provided 335.0 mg (61.6%) **126i** as a yellow oil.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.17(1H, s), 3.90(3H, s), 3.92(3H, s), 5.23(1H, d, J = 2.64 Hz), 5.85(1H, d, J = 2.64 Hz), 6.73(2H, d, J = 7.3 Hz), 6.85(1H, d, J = 8.4 Hz), 6.97-7.00(2H, m), 7.10-7.29(6H, m), 7.41(1H, s), 7.48(1H, d, J = 1.9 Hz); IR(KBr)υ: 3063, 3031, 3006, 2974, 2935, 2908, 2836, 1747, 1707, 1600, 1515, 1455, 1341, 1272, 1258, 1221, 1146, 1027 cm^{-1}; $[\alpha]_D^{25}$ = -109.5 ° (c = 1.2, CH_2Cl_2); Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.86; H, 6.49; N, 2.54.

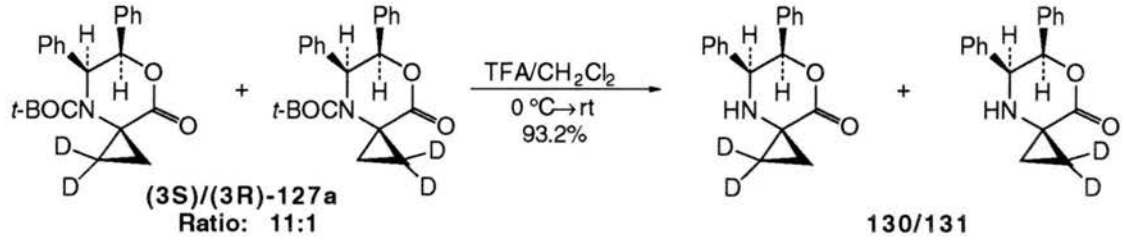


126a (3S)/(3R)-127a Ratio: 11:1

(3S, 5S, 6R)- and (3R,5S,6R)-4-(*tert*-butoxycarbonyl)-1,1-dideutero-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octa-8-one ((3S)/(3R)-127a).[93]

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.05 g, 3.52 mmol, 1.5 equiv) and 50 % NaH dispersion (168.9 g, 3.52 mmol, 1.5 equiv) was added DMSO (5 mL) at room temperature. The reaction was stirred for 1.0 h and then the freshly prepared ylide was added via cannula to a partially frozen slurry of **126a** (862 mg, 2.35 mmol, 1.0 equiv) in DMSO (5 mL). The reaction was slowly warmed to room temperature and stirred for 4 days. To the mixture was added brine (3 mL), followed by extraction with 4 x 5 mL EtOAc. The organic fractions were combined, washed with several portions of H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (6.7 g silica, eluted with 1:10 EtOAc/Hexanes) provided 856.4 mg (95.7%) of white crystalline **(3S)/(3R)-127a** in an 11:1 ratio:

^{1}H NMR(300 MHz)(DMSO-d_6)δTMS: 1.17(9H, s), 1.40(d, J = 4.7 Hz) and 1.53(d, J = 4.9 Hz)(1H), 1.82-1.86(1H, m), 5.47(1H, d, J = 3.0 Hz), 6.30(1H, d, J = 3.3 Hz), 6.80-6.83(2H, m), 7.12-7.31(8H, m); IR(KBr)υ: 3109, 3090, 3065, 3034, 3004, 2985, 2932, 1954, 1889, 1736, 1705, 1570, 1560, 1455, 1387, 1353, 1297, 1282, 1269, 1154, 1066 cm^{-1}; $[\alpha]_D^{25}$ = + 52.6 ° (c = 1.0, CH_2Cl_2); mp = 110 - 112 °C; Anal.(recrystallized from EtOH). Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.74; H, 6.63; N, 3.70.

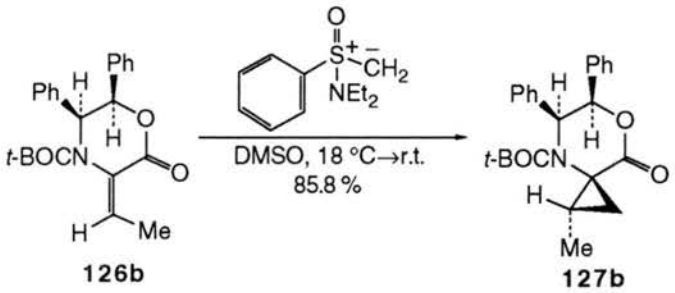


(3S,5S,6R)- and (3R,5S,6R)-1,1-dideutero-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octa-8-one (130/131).

To a 0 °C solution of **(3S)/(3R)-127a** (93.5 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (378 µL, 4.90 mmol, 20 equiv). The mixture was allowed to slowly warm to room temperature while stirring for 24 h. Solvent and excess TFA were removed *in vacuo* , and the crude trifluoroacetate salt redissolved in CH_2Cl_2 (5 mL) followed by addition of Et_3N. The solution was washed with H_2O (to

remove triethylammonium trifluoroacetate), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (3g silica, eluted with 1:10 EtOAc/Hexanes) provided 64.3 mg (93.2%) of white crystalline **130/131** in an 11:1 ratio:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.14(d, J = 3.3Hz) and 1.21(d, J = 4.4 Hz)(1H), 1.49(d, J = 3.3 Hz) and 1.81(d, J = 4.4 Hz)(1H), 2.64(1H, broad s), 4.84(1H, d, J = 3.8 Hz), 5.90(1H, d, J = 3.8 Hz), 6.74-6.87(4H, m), 7.15-7.27(6H, m); IR(NaCl, neat)υ: 3313, 3087, 3067, 3026, 2964, 2923, 2872, 1723, 1600, 1451, 1374, 1128, 1062, 1021 cm^{-1}; $[\alpha]^{25}_D$ = +244.0° (c = 1.0, CH_2Cl_2); mp = 132-133 °C; Anal.(recrystallized from EtOH) Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.26; H, 6.09; N, 5.03.

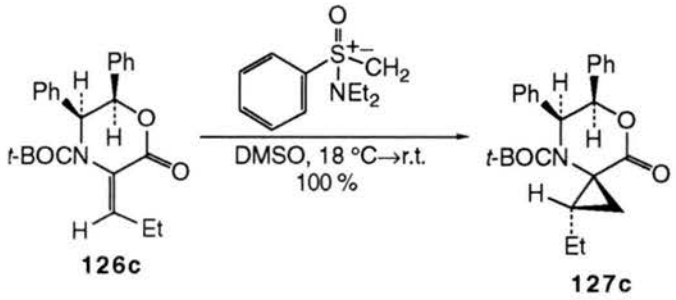


(1S,3S,5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-1-methyl-7-oxa-4-azaspiro[2.5]octa-8-one (127b).

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.65 g, 5.51 mmol, 2.0 equiv) and 50% dispersion (264.3 mg, 5.55 mmol, 2.0 equiv) was added DMSO (8 mL) at room temperature. After stirring for 1 h the ylide solution was added via cannula to a partially frozen slurry of **126b** (1.04 g, 2.75 mmol, 1.0 equiv) in DMSO (8 mL) at ~ 18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added brine (4 mL), followed by extraction with 3 x 5 mL EtOAc. The organic fractions were combined, washed thoroughly with H_2O to remove DMSO, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (30 g silica, eluted with 1:10 EtOAc/Hexanes) provided 928.8 mg (85.8%) of **127b** as a white crystalline solid:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.06(9H, s), 1.20(3H, d, J = 5.7 Hz), 1.72(2H, m), 2.67(1H, broad s), 5.18(1H, broad s), 5.88(1H, d, J = 3.3 Hz), 6.77(2H, d, J = 7.2 Hz), 7.00-7.26(8H, m); IR(KBr)υ: 3109, 3089, 3065, 3032, 3006, 2980, 2930,1754,

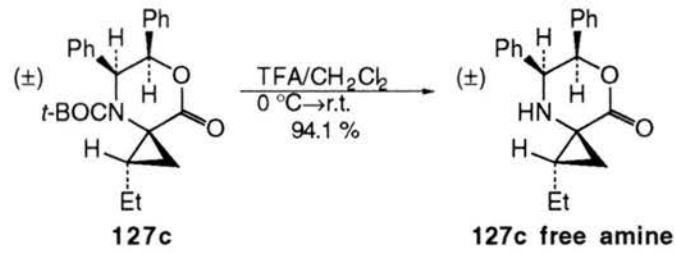
1713, 1705, 1458, 1386, 1365, 1162, 1152, 1103, 1079, 1064 cm^{-1}; $[\alpha]_D^{25}$ = +11.49 ° (c = 1.0, CH_2Cl_2); mp = 155-157 °C; Anal.(recrystallized from EtOH/Hexanes) Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.20; H, 6.90; N, 3.42.



(1S,3S,5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-1-ethyl-7-oxa-4-azaspiro[2.5]octa-8-one (127c).

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (152 mg, 0.51 mmol, 2.0 equiv) and 50% NaH dispersion (24.4 mg, 0.51 mmol, 2.0 equiv) was added DMSO (2 mL) at room temperature. After stirring 1 h, the ylide solution was added via cannula to a partially frozen slurry of **126c** (100 mg, 0.25 mmol, 1.0 equiv) in DMSO (2 mL) at 18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added brine (2 mL), followed by extraction with 3 x 5 mL EtOAc. The organic fractions were combined, washed repeatedly with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (9.9 g silica, eluted with 1:10 EtOAc/Hexanes) provided 104 mg (100%) **127c** as a white crystalline solid:

^1H NMR (300 MHz)($CDCl_3$)δTMS: 1.03-1.31(13H, m), 1.59-1.80(3H, m), 2.74(1H, broad s), 5.20(1H, apparent s), 5.96(1H, d, J = 3.2 Hz), 6.74-6.77(2H, m), 6.99-7.28(8H, m); IR(KBr)υ: 3091, 3033, 3009, 2961, 2935, 1751, 1706, 1457, 1386, 1365, 1243, 1155, 1100, 1063 cm^{-1}; $[\alpha]_D^{20}$ = +20.5 ° (c = 1.0, CH_2Cl_2); mp = 178-180 °C; Anal. (recrystallized from EtOH). Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.61; H, 7.10; N, 3.48.

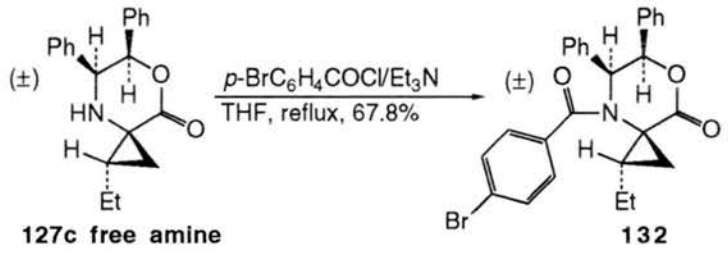


127c **127c free amine**

(±)-5,6-diphenyl-E-1-ethyl-7-oxa-4-azaspiro[2.5]octa-8-one (127c free amine).

To a 0 °C solution of **(±)-127c** (486.7 mg, 1.19 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added TFA (1.8 mL, 23.89 mmol, 20 equiv). The mixture was allowed to warm to room temperature and stirred for 21 h. Solvent and excess TFA were removed *in vacuo* and the crude trifluoroacetate salt redissolved in CH_2Cl_2. The resulting solution was washed with H_2O (to remove triethylammonium trifluoroacetate), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (22 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) provided 345.4 mg (94.1%) of the free amine of **(±)-127c** as a white crystalline solid:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.05(3H, t, J = 7.3 Hz), 1.29-1.34(1H, m), 1.40-1.48(1H, m), 1.51-1.68(3H, m), 2.42(1H, broad d, J = 7.8 Hz), 4.75(1H, broad d, J = 4.4 Hz), 5.86(1H, d, J = 4.2 Hz), 6.78-6.89(4H, m), 7.14-7.25(6H, m); IR(KBr)υ: 3304, 3089, 3065, 3029, 2967, 2929, 2825, 1704, 1452, 1363, 1151, 1022 cm^{-1}; mp = 113-115 °C; Anal.(recrystallized from EtOH) Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.31; H, 6.78; N, 4.59.

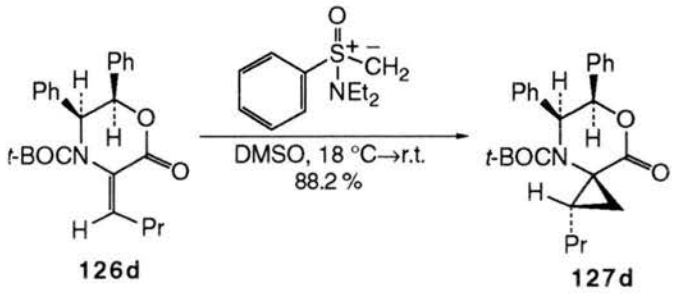


127c free amine **132**

(±)-5,6-diphenyl-E-1-ethyl-4-(4'-bromobenzoyl)-7-oxa-4-azaspiro[2.5]octa-8-one (132).

To a solution containing (±)-5,6-diphenyl-E-1-ethyl-7-oxa-4-azaspiro[2.5]octa-8-one (50.0 mg, 0.16 mmol, 1.0 equiv) and 4-bromobenzoyl chloride (71.4 mg, 0.33 mmol, 2.0 equiv) in THF (5 mL) was added Et_3N (45.4 μL, 0.33 mmol, 2.0 equiv). The resulting mixture was refluxed for 14 h, cooled to room temperature, and the solvent removed *in vacuo*. The crude solid was purified via flash chromatography (8 g silica, eluted with 1:10-1:1 EtOAc/Hexanes) to provide 54.1 mg (67.8%) **132** as a white crystalline solid:

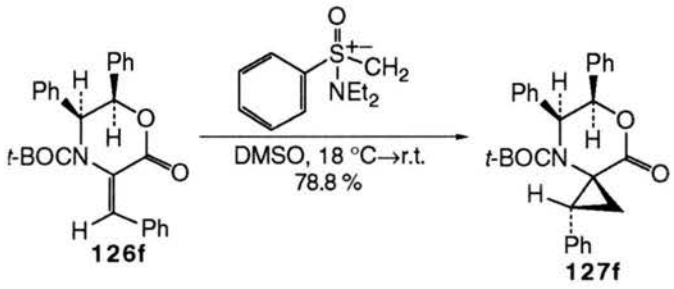
^1H NMR (300 MHz)($CDCl_3$) δTMS: 1.03(3H, t, J = 6.9 Hz), 1.10-1.22(1H, m), 1.35-1.82(4H, m), 5.34(1H, broad s), 6.09(1H, d, J = 4.0 Hz), 6.78(2H, broad d, J = 6.3 Hz), 6.90-7.23(10H, m), 7.45(2H, d, J = 8.2 Hz); IR(KBr)υ: 3093, 3069, 3032, 2963, 2931, 2878, 2861, 1752, 1660, 1589, 1453, 1305, 1158, 1142, 1049 cm^{-1}; mp = 204-205 °C; Anal.(recrystallized from EtOH) Calcd for $C_{27}H_{24}NO_3$: C, 66.13; H, 4.93; N, 2.86. Found: C, 66.08; H, 5.01; N, 2.82. A single crystal x-ray analysis of this compound has been solved (Figure 12).[67]



(1S,3S,5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-1-propyl-7-oxa-4-azaspiro[2.5]octa-8-one (127d).

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (880.9 mg, 2.95 mmol, 2.0 equiv) and 50% NaH dispersion (141.3 mg, 2.95 mmol, 2.0 equiv) was added DMSO (4 mL) at room temperature. After stirring 1 h, the ylide solution was added via cannula to a partially frozen slurry of **126d** (600 mg, 1.47 mmol, 1.0 equiv) in DMSO (4 mL) at ~ 18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added H_2O (5 mL) followed by extraction with 3 x 5 mL EtOAc. The organic fractions were washed thoroughly with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (35 g silica, eluted with 1:10 EtOAc/Hexanes) provided 547.2 mg (88.2%) **127d** as a white crystalline solid:

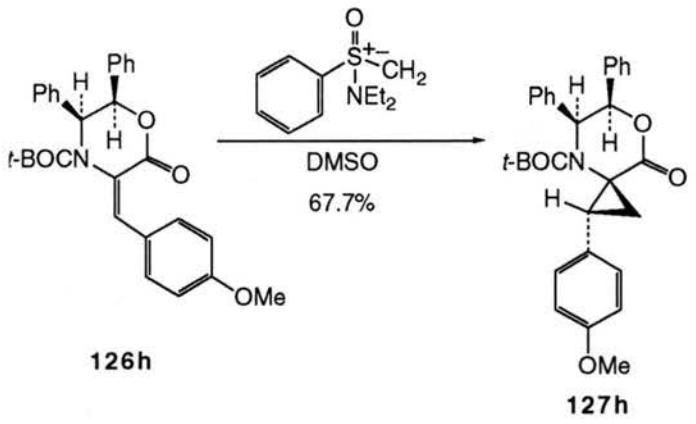
^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 0.95(3H, t, J = 7.3 Hz), 1.07(9H, s), 1.15-1.23(1H, m), 1.42-1.55(2H, m), 1.58-1.66(1H, m), 1.72-1.80(2H, m), 2.75(1H, broad s), 5.19(1H, broad s), 5.93(1H, d, J = 3.2 Hz), 6.72(2H, m), 6.99-7.24(8H, m); IR(KBr)υ: 3090, 3069, 3032, 3009, 2997, 2965, 2930, 2875, 1750, 1708, 1459, 1387, 1365, 1162, 1103, 1047 cm^{-1}; $[\alpha]_D^{25}$ = +30.0 ° (c = 1.0, CH_2Cl_2); mp = 179-180 °C; Anal.(recrystallized from EtOH) Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41, N, 3.32. Found: C, 73.90; H, 7.41; N, 3.15.



(1S,3S,5S,6R)-4-(tert-butoxycarbonyl)-1,5,6-triphenyl-7-oxa-4-azaspiro[2.5]octa-8-one (127f).

To a solid mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.08 g, 3.62 mmol, 2.0 equiv) and 50% NaH dispersion (87 mg, 3.62 mmol, 2.0 equiv) was added DMSO (5 mL). The mixture was vigorously stirred for 1 h and then was added via cannula to an 18 °C slurry of **126f** (800 mg, 1.81 mmol, 1.0 equiv) in DMSO (5 mL). The reaction was allowed to slowly warm to room temperature over several hours and stirred for 4 days, followed by quenching with brine and extraction with 3 x 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished via recrystallization of the crude material from hot EtOH/THF, providing 650.4 mg (78.8%) **127f** as fine white needles:

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 1.06(9H,s), 2.66(1H, dd, J_{gem} = 9.3 Hz, J_{vic} = 2.0 Hz), 2.92(1H, t, J = 9.6 Hz), 3.27(1H, broad t, J = 8.3 Hz), 5.17(1H, d, J = 3.1 Hz), 5.86(1H, d, J = 3.1 Hz), 6.71-6.75(2H, m), 6.85-6.88(2H, m), 7.06-7.33(11H, m). IR(KBr) υ: 3096, 3063, 3030, 2976, 2932, 1954, 1889, 1741, 1703, 1605, 1458, 1382, 1360, 1158, 1088, 1060 cm^{-1}; $[\alpha]_D^{25}$ = + 179.3 ° (c = 1.0, CH_2Cl_2); mp = 235-236 °C (dec.); Anal.(recrystallized from EtOH/THF) Calcd for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.44; H, 6.42; N, 3.07.



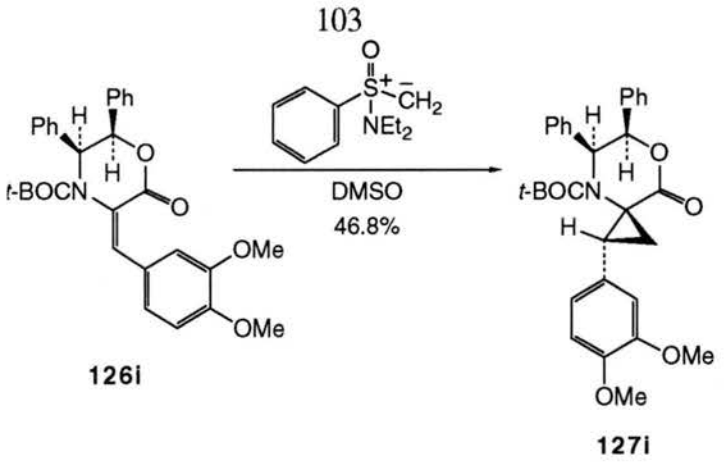
126h

127h

(1S,3S,5S,6R)-4-(*tert*-butoxycarbonyl)-1-(4'-methoxyphenyl)-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octa-8-one (127h).

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (304.5 mg, 1.02 mmol, 2.0 equiv) and degreased NaH (24.4 mg, 1.02 mmol, 2.0 equiv) was added DMSO (4.5 mL) at room temperature. After stirring 1h, the ylide solution was added via cannula to a partially frozen slurry of **126h** (240.0 mg, 0.51 mmol, 1.0 equiv). The reaction was slowly warmed to room temperature and stirred for 3 days. To the mixture was added EtOAc (10 mL) and the resulting solution was washed repeatedly with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR of the crude product showed that only a single diastereomer was obtained. Purification via crystallization from EtOH/THF provided 167.7 mg (67.7 %) **127h** as fine white needles.

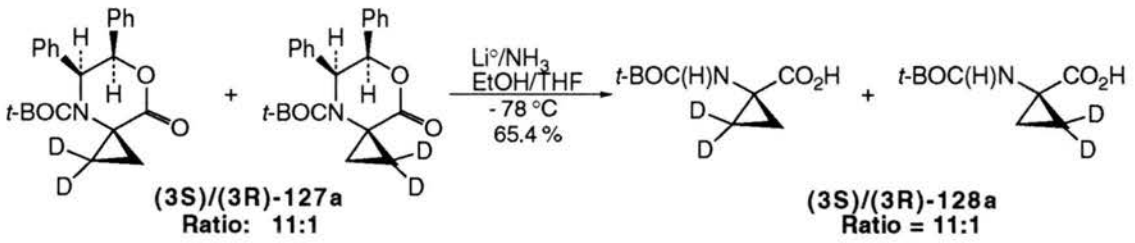
^1H NMR(300 MHz)($CDCl_3$)δTMS: 1.06(9H, s), 2.59(1H, dd, J_{gem} = 9.2 Hz, J_{vic} = 1.9 Hz), 2.87(1H, apparent t, J = 9.5 Hz), 3.22(1H, apparent t, J = 8.3 Hz), 3.73(3H, s), 5.16(1H, d, J = 3.2 Hz), 5.86(1H, d, J = 3.2 Hz), 6.73(2H, d, J = 7.0 Hz), 6.81-6.88(4H, m), 7.06-7.22(8H, m); IR(KBr)υ: 3068, 3032, 3008, 2977, 2932, 2837, 1750, 1703, 1516, 1383, 1357, 1251, 1159, 1060 cm^{-1}; $[\alpha]_D^{25}$ = + 199.4 ° (c = 1.0, CH_2Cl_2); mp = 215-217 °C. Anal.(recrystallized from EtOH). Calcd for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.43; N, 2.88. Found: C, 74.39; H, 6.61; N, 2.88.



(1S,3S,5S,6R)-4-(*tert*-butoxycarbonyl)-1-(3',4'-dimethoxyphenyl)-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octa-8-one (127i).

To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (76.0 mg, 0.25 mmol, 1.5 equiv) and degreased NaH (6.1 mg, 0.25 mmol, 1.5 equiv) was added DMSO (1 mL) at room temperature. After stirring 1h, the ylide solution was added via cannula to a room temperature slurry of **126i** (85.0 mg, 0.17 mmol, 1.0 equiv). The reaction was stirred for 3 days. To the mixture was added EtOAc (5 mL) and the resulting solution was washed repeatedly with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR of the crude product showed that two diastereomers were obtained in a ratio of 9.9:1.0. Purification via crystallization from EtOH provided 40.9 mg (46.8 %) of diastereomerically pure **127i** as fine white needles.

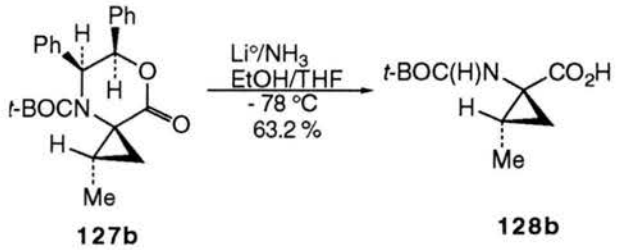
^1H NMR(300 MHz)($CDCl_3$)δTMS: 1.06(9H, s), 2.59(1H, dd, J_{gem} = 9.2 Hz, J_{vic} = 1.7 Hz), 2.85(1H, apparent t, J = 9.6 Hz), 3.25(1H, apparent t, J = 8.4 Hz), 3.80(3H, s), 3.86(3H, s), 5.16(1H, d, J = 3.0 Hz), 5.87(1H, d, J = 3.1 Hz), 6.72-6.87(7H, m), 7.07-7.26(6H, m); IR(KBr)υ: 3067, 3031, 2977, 2935, 2836, 1746, 1708, 1697, 1519, 1389, 1384, 1367, 1254, 1243, 1159, 1140, 1060, 1028 cm^{-1}; $[\alpha]_D^{25}$ = + 195.6 ° (c = 1.0, CH_2Cl_2); mp = 203-205 °C. Anal.(recrystallized from EtOH). Calcd for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.29; H, 6.70; N, 2.60.



(1S)- and (1R)-1-(N-(*tert*-butoxycarbonyl)amino-2,2-dideuterocyclopropane-1-carboxylic acid ((3S)/(3R)-128a).

To a - 78 °C solution containing **(3S)/(3R)-127a** (557.2 mg, 1.46 mmol, 1.0 equiv) and anhydrous EtOH (857.2 μL, 14.6 mmol, 10.0 equiv) in THF (29.2 mL) and NH_3 (146 mL) was added lithium metal (~ 132 mg) in small pieces until a persistent blue color was obtained. The mixture was stirred an additional 5 min and then immediately quenched with solid NH_4Cl until the suspension turned snow white. The reaction was allowed to warm to room temperature and the NH_3 evaporated completely. The white residue was dissolved in a minimum amount of H_2O, washed with 3 x 5 mL Et_2O, and carefully acidified to pH 2.5 with 2 N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 194.1 mg (65.4 %) **(3S)/(3R)-128a** as a white crystalline solid:

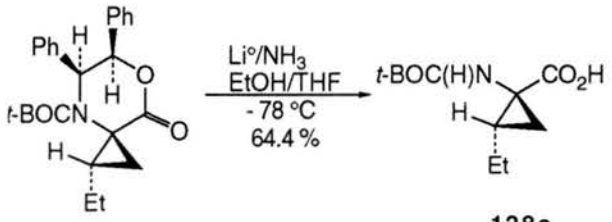
^1H NMR (300 MHz)($CDCl_3$)δTMS: 1.03(1H, d, J = 4.5 Hz), 1.46(9H, s), 1.55(1H, d, J = 4.6 Hz), 6.31(2H, broad s); IR(KBr)υ: 3489, 3239, 3128, 3002, 2976, 2936, 1707, 1687.0, 1658, 1602, 1394, 1375, 1366, 1172, 1073, 1053, 1026 cm^{-1}; mp = 161-162 °C (recrystallized from EtOH/Hexanes).



(1S,2S)-1-(N-(*tert*-butoxycarbonyl)amino)-2-methylcyclopropane-1-carboxylic acid (128b).

To a - 78 °C solution containing **127b** (925 mg, 2.35 mmol, 1.0 equiv), anhydrous EtOH (1.4 mL, 23.51 mmol, 10.0 equiv), THF (26 mL), and NH_3 (168 mL) was added Li° pieces until a persistent blue color appeared. After the NH_4Cl quench, the reaction was allowed to warm to room temperature and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 x 5 mL Et_2O, and carefully acidified to pH 2.5 with 2N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 319.6 mg (63.2%) of **128b** as a white crystalline solid:

^1H NMR (CD_3OD)δTMS: 1.21(1H, dd, J_{vic} = 4.8 Hz, J_{gem} = 9.4 Hz), 1.23(3H, d, J = 6.3 Hz), 1.29-1.35(1H, m), 1.43-3.34(10H, m), 4.89(2H, s); IR(KBr)υ: 3303, 3253, 3094, 3011, 2978, 2936, 2883, 2697, 2578, 2494, 1701, 1654, 1648, 1410, 1367, 1203, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +38.1 ° (c = 1.0, CH_3OH); mp = 182-183 °C; Anal.(recrystallized from EtOH/Hexanes) Calcd for $C_{10}H_{17}HNO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.00; H, 8.14; N, 6.57.

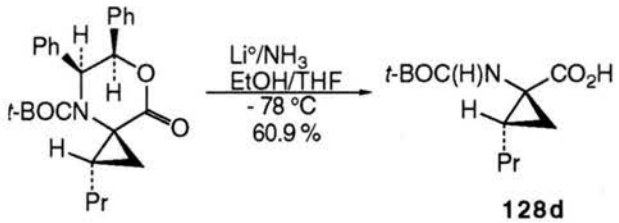


127c **128c**

(1S,2S)-1-(N-(*tert*-butoxycarbonyl)amino)-2-ethylcyclopropane-1-carboxylic acid (128c).

To a - 78 °C solution containing **127c** (559.4 mg, 1.37 mmol, 1.0 equiv), anhydrous EtOH (805.6 µL, 13.73 mmol, 10.0 equiv), THF (15 mL), and NH_3 (98 mL) was added Li° (~124 mg) until the persistent blue color was observed. After the NH_4Cl quench, the reaction was allowed to warm to room temperature and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 x 5 mL Et_2O, and carefully acidified to pH 2.5 with 2N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 202.7 mg (64.4%) of **128c** as a white crystalline solid:

^{1}H NMR (CD_3OD)δTMS: 0.98(3H, t, J = 7.4 Hz), 1.12-1.17(1H, m), 1.39-1.48(11H, m), 1.54-1.63(2H, m), 4.88(2H, broad s); IR(KBr)υ: 3303, 3253, 3100, 2975, 2936, 2878, 2697, 2583, 2492, 1700, 1649, 1478, 1458, 1410, 1397, 1368, 1306, 1200, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +33.3 ° (c = 1.0, CH_3OH); mp = 126-127 °C; Anal.(recrystallized from EtOH/Hexanes) Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.71; H, 8.41; N, 6.19.

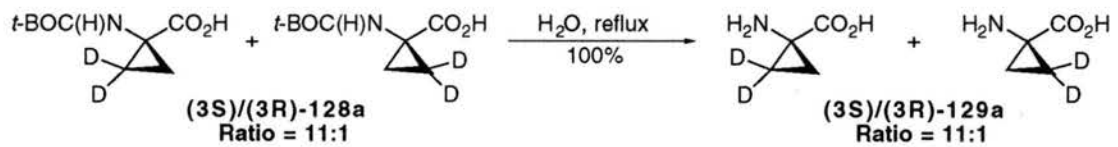


127d **128d**

(1S,2S)-1-(N-(*tert*-butoxycarbonyl)amino)-2-propylcyclopropane-1-carboxylic acid (128d)

To a - 78 °C solution containing **127d** (545 mg, 1.29 mmol, 1.0 equiv), anhydrous EtOH (1.2 mL, 20.47 mmol, 15.9 equiv), THF (19 mL), and NH_3 (92 mL) was added Li° until the persistent blue discharge was observed. After the NH_4Cl quench, the reaction was allowed to warm to room temperature and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 x 5 mL Et_2O, and carefully acidified to pH 2.5 with 2N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 191.5 mg (60.9%) of **128d** as a white crystalline solid:

^{1}H NMR (CD_3OD)δTMS: 0.93(3H, t, J = 7.2 Hz), 1.14(1H, m), 1.33-1.59(15H, m), 4.87(2H, broad s); IR(KBr)υ: 3295, 3247, 3096, 2981, 2962, 2933, 2875, 2702, 2583, 2494, 1698, 1655, 1649, 1401, 1368, 1202, 1167, 1062, cm^{-1}; $[\alpha]^{25}_D$ = + 41.8 ° (c = 1.0, MeOH); mp = 118-119 °C; Anal.(recrystallized from EtOH/Hexanes) Calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.49; H, 8.77; N, 5.84.

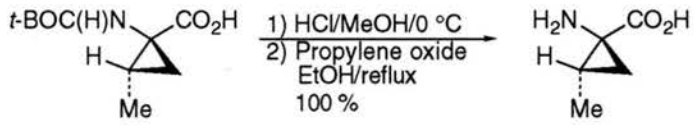


(3S)/(3R)-128a Ratio = 11:1 **(3S)/(3R)-129a Ratio = 11:1**

(1S)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acid ((3S)/(3R)-129a).

A suspension of **(3S)/(3R)-128a** in H_2O (3 mL) was heated to reflux for 12 h. After cooling, the reaction mixture was eluted on a C_{18} reverse phase Sep-pak cartridge. Evaporation of solvent provided 17.2 mg (100%) **(3S)/(3R)-129a** as a white crystalline solid. No further purification was necessary:

^1H NMR (300 MHz)(D_2O)δHOD: 1.04(1H, d, J = 5.9 Hz), 1.18(1H, d, J = 5.9 Hz); IR(KBr)υ: 3430, 3017, 2732, 2634, 2545, 2113, 1791-1462, 1403, 1324, 1241 cm^{-1}; mp = sublimes > 200 °C, 237-239 °C (dec).

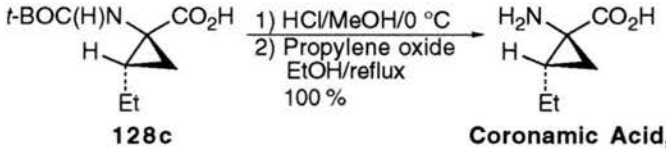


128b **Norcoronamic Acid, 3**

(1S,2S)-2-Methylcyclopropane-1-carboxylic Acid (Norcoronamic Acid, 3).

To a 0 °C solution of 1N HCl in MeOH (18.6 mL, 18.6 mmol, 40.0 equiv) was added **128b** (100 mg, 0.47 mmol, 1.0 equiv). The mixture was stirred for 29 h at 0 °C, followed by removal of the solvent. To the white crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (~ 2 mL) and eluted through a C_{18} reverse phase Sep-pak cartridge which, after removal of H_2O, provided 54 mg (100%) of norcoronamic acid (**3**) as a white crystalline solid:

^1H NMR (300 MHz)(D_2O)δHOD: 1.03-1.19(2H, m), 1.05(3H, d, J = 6.2 Hz), 1.32-1.46(1H, m); IR(KBr)υ: 3435, 3009, 2739, 2090, 1739, 1586, 1438, 1404, 1301, 1222, 1173, 1051 cm^{-1}; $[\alpha]_D^{25}$ = + 50.9 ° (c = 1.0, H_2O); $[\alpha]_D^{20}$ (lit.)[61] = + 44 ° (c = 1.0, H_2O); mp = sublimes > 205 °C.

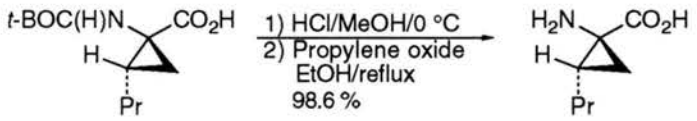


128c **Coronamic Acid, 2**

(1S,2S)-2-Ethylcyclopropane-1-carboxylic Acid (Coronamic Acid, 2).

To a 0 °C solution of 1N HCl in MeOH (17.5 mL, 17.5 mmol, 40.0 equiv) was added **128c** (100 mg, 0.45 mmol, 1.0 equiv). The mixture was stirred for 24 h at 0 °C, followed by removal of the solvent. To the white crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (2 mL) and eluted through a C_{18} reverse phase Sep-pak cartridge which, after removal of H_2O, provided 56.0 mg (100%) of coronamic acid (**2**) as a white crystalline solid:

^{1}H NMR (300 MHz)(D_2O)δHOD: 0.79(3H, t, J = 7.2 Hz), 1.15(2H, apparent d, J = 8.3 Hz), 1.28-1.54(3H, m); IR(KBr)υ: 3444, 2967, 2932, 2878, 2094, 1600(br), 1398, 1295, 1218, 1175, 1044 cm^{-1}; $[\alpha]^{25}_D$ = +14.5 ° (c = 1.67, H_2O); $[\alpha]^{25}_D$ (lit.)[14b] = +14.7 ° (c = 1.67, H_2O); mp = sublimes > 185 °C.



128d **129d**

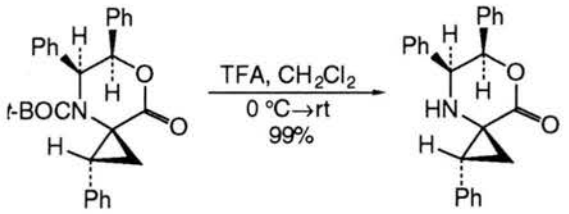
(1S,2S)-2-Propylcyclopropane-1-carboxylic Acid (129d).

To a 0 °C solution of 1N HCl in MeOH (16.4 mL, 16.4 mmol, 40.0 equiv) was added **128d** (100 mg, 0.41 mmol, 1.0 equiv). The mixture was stirred for 24 h at 0 °C, followed by removal of the solvent. To the crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was heated to reflux for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (2 mL) and eluted through a C_{18} reverse phase Sep-pak cartridge which, after removal of H_2O, provided 58.0 mg (98.6%) of **129d** as a white crystalline solid:

^{1}H NMR (300 MHz)(D_2O)δHOD: 0.74(3H, t, J = 7.3 Hz), 1.14-1.49(7H, m); IR(KBr)υ: 3433, 2959, 2930, 2874, 2071, 1594(br), 1442, 1404, 1300, 1273, 1213, 1175, 1049 cm^{-1}; $[\alpha]^{25}_D$ = +26.1 ° (c = 1.0, H_2O); mp = sublimes > 200 °C; Anal.(recrystallized from H_2O/acetone) Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 59.00; H, 8.92; N, 9.71.

General Procedure for the Preparation of Mosher Amides of Amino Acids 2,3, and 129d.[75]

To a stirred suspension of **2** (5 mg, 0.04 mmol, 1.0 equiv) in THF (1 mL) was added (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (11.0 mg, 0.04 mmol, 1.0 equiv) and propylene oxide (12.2 mL, 0.17 mmol, 4.0 equiv). The resulting mixture was heated to reflux for 0.5 h, cooled to room temperature, and thoroughly evaporated to provide the corresponding MTPA amide as a crude oil. In similar fashion, racemic α-methoxy-α-(trifluoromethyl)phenyl acetic acid was reacted with **2** to form the corresponding diastereomeric MTPA amides as a crude oil. The % ee was determined by ^{19}F NMR analysis of the trifluoromethyl signal of the MTPA amides. The same procedure was used for the % ee analyses of **3** and **129d**.



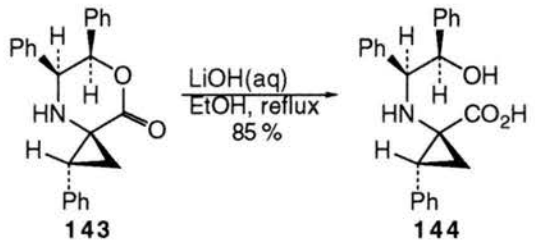
127f **143**

(1S,3S,5S,6R)-1,5,6-Triphenyl-7-oxa-4-azaspiro[2.5]octa-8-one (143).

To a 0 °C solution containing **127f** (398.0 mg, 0.87 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added TFA (1.35 mL, 17.47 mmol, 20.0 equiv). The reaction was slowly warmed to room temperature and stirred an additional 17 h. The solvent and excess TFA were removed in vacuo and the crude residue was redissolved in CH_2Cl_2 (15 mL) and washed with dilute $NaHCO_3$ (aq). The layers were separated and the aqueous layer extracted with 2 x 5 mL CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to provide 306.8 mg (98.8%) **143** as a light yellow solid. The crude product can be carried on without further purification.

^1H NMR(300 MHz)($CDCl_3$)δTMS: 1.68(1H, dd, J_{gem} = 9.5 Hz, J_{vic} = 3.9 Hz), 2.35(1H, dd, J_{gem} = 8.3 Hz, J_{vic} = 2.7 Hz), 2.55(1H, d, J = 8.2 Hz), 2.80(1H, apparent t, J = 8.9 Hz), 4.86(1H, dd, J_{gem} = 8.2 Hz, J_{vic} = 4.0 Hz), 5.81(1H, d, J = 4.1 Hz), 6.81-6.84(2H, m), 6.90-6.94(2H, m), 7.12-7.33(11H, m); IR(KBr)υ: 3357, 3085,

3063, 3030, 2965, 2921, 2889, 1959, 1889, 1736, 1605, 1496, 1453, 1316, 1251, 1213, 1142, 1082, 1049 cm^{-1}; $[\alpha]_D^{25}$ = +299.5 ° (c = 1.0, CH_2Cl_2); mp = 165-166 °C. Anal. (recrystallized from EtOH). Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.95; N, 3.94. Found: C, 80.87; H, 5.77; N, 3.94.

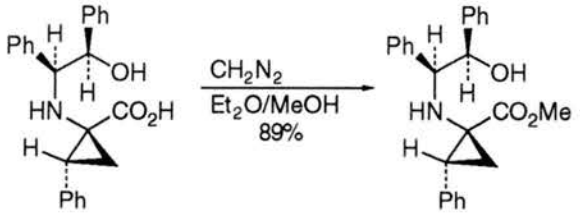


143 **144**

(1S,2R,1'S,2'R)-1-(N-(1',2'-diphenyl-2'-hydroxyethyl)amino)-2-phenylcyclopropane-1-carboxylic acid (144).

A mixture containing **143** (340.0 mg, 0.96 mmol, 1.0 equiv), $LiOH{\cdot}H_2O$ (52.2 mg, 1.24 mmol, 1.3 equiv), EtOH (5 mL), and H_2O (5 mL) was heated to reflux for 0.5 h. The reaction was cooled to room temperature and 2M HCl (aq) was added until a thick white precipitate formed. The crude product was collected via Buchner filtration and washed thoroughly with H_2O, providing 302.3 mg (84.6%) **144** as a white amorphous solid.

^1H NMR(300 MHz)(DMSO-d_6)δTMS: 1.33(1H, dd, J_{gem} = 9.4 Hz, J_{vic} = 4.8Hz), 1.70(1H, dd, J_{gem} = 8.0 Hz, J_{vic} = 4.7 Hz), 2.32(1H, apparent t, J = 8.7 Hz), 4.12(1H, d, J = 4.8 Hz), 4.90(1H, d, J = 4.8 Hz), 6.96(2H, d, J = 6.9 Hz), 7.07-7.25(13H, m); IR(KBr)υ: 3424, 3268, 3089, 3062, 3029, 2873, 2780, 1952, 1886, 1630, 1604, 1569, 1498, 1454, 1390, 1353, 1327, 1190, 1099, 1066 cm^{-1}; $[\alpha]_D^{25}$ = +82.4 ° (c = 0.5, 1M NaOH); mp = 201-202 °C. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.93; H, 6.31; N, 3.61.

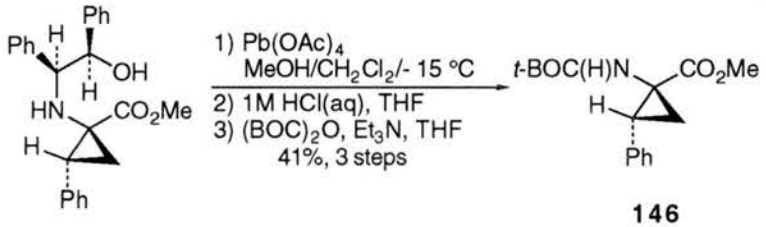


144 **145**

(1S,2R,1'S,2'R)-Methyl 1-(N-(1',2'-Diphenyl-2'-hydroxyethyl)amino)-2-phenylcyclopropane-1-carboxylate (145).

To a 0 °C slurry containing 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) (439.6 mg, 3.0 mmol, 6.0 equiv) and Et_2O (6 mL) was added approximately 1 mL 5N NaOH. The mixture was stirred for 20 min at which time the ethereal CH_2N_2 solution was separated and added to a room temperature suspension of **144** (186.0 mg, 0.50 mmol, 1.0 equiv) in MeOH (2 mL). The reaction was allowed to stir overnight in an open flask and the crude ester was concentrated to dryness and purified via flash silica chromatography (10 g silica, 1:5 EtOAc/hexanes) providing 171.4 mg (88.8%) **145** as a white solid.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.41(1H, dd, J_{gem} = 9.6 Hz, J_{vic} = 4.5 Hz), 1.98(1H, dd, J_{gem} = 7.9 Hz, J_{vic} = 2.7 Hz), 2.57(1H , apparent t, J = 8.8 Hz), 2.69(1H, s), 3.14(3H, s), 3.60(1H, d, J = 3.9 Hz), 4.28(1H, d, J = 5.0 Hz), 4.97(1H, t, J = 4.5 Hz), 6.99-7.01(2H, m), 7.07-7.26(13H, m); IR(KBr)υ: 3426, 3339, 3236, 3086, 3063, 3029, 2956, 2918, 1734, 1452, 1319, 1215, 1199, 1154, 1061 cm^{-1}; $[\alpha]_D^{25}$ = +128.4 ° (c = 1.0, CH_2Cl_2); mp = 142-143 °C. Anal. (recrystallized from EtOH). Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.31; H, 6.41; N, 3.65.



145 **146**

(1S,2R)-Methyl 1-(N-(*tert*-butoxycarbonyl)amino-2-phenylcyclopropane-1-carboxylate (146).

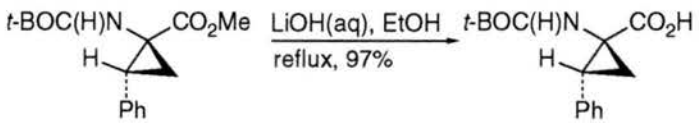
To a - 15 °C solution containing **145** (61.9 mg, 0.16 mmol, 1.0 equiv) and a 1:2 mixture of MeOH/CH_2Cl_2 (3 mL) was added $Pb(OAc)_4$ (77.9 mg, 0.18 mmol, 1.1 equiv). The reaction was complete in 2 min and subsequently quenched with saturated $NaHCO_3$ (5 mL) at - 15 °C. A heavy white precipitate formed and was removed via Buchner filtration. The filter cake was washed thoroughly with CH_2Cl_2 (10 mL) and the filtrate layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 5 mL) and the organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated. Crude yield of

the acid sensitive imine was 50.7 mg (> 100%, contaminated by benzaldehyde and minor impurities) isolated as a clear oil.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.82-1.87(1H, m), 2.41-2.46(1H, m), 2.94(1H, apparent t, J = 8.8 Hz), 3.39(3H, s), 7.19-7.44(10H, m), 8.48(1H, s).

To a room temperature solution of the crude imine (44.6 mg based on theoretical yield, 0.16 mmol, 1.0 equiv) in THF (5 mL) was added 1 M HCl(aq) (5 mL). After stirring for 15 min the reaction was concentrated to dryness and thoroughly dried under high vacuum overnight. To the crude hydrochloride salt in THF (5 mL) at room temperature was added Et_3N (33.4 μL, 0.24 mmol, 1.5 equiv). Immediately a fine white suspension formed and the slurry was cooled to 0 °C followed by the addition of di-*tert*-butyldicarbonate (38.3 mg, 0.18 mmol, 1.1 equiv). The reaction was warmed to room temperature and stirred for 24 h. At this time EtOAc (5 mL) was added to the reaction followed by washing of the solution with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography (96:4 CH_2Cl_2/MeOH) provided 19.0 mg(40.8% from **145**) **146** as a clear viscus oil.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.49(9H, s), 1.61(1H, dd, J_{gem} = 9.6 Hz, J_{vic} = 4.2 Hz), 2.18(1H, dd, J_{gem} = 8.4 Hz, J_{vic} = 2.9 Hz), 3.35(3H, s), 5.33(1H, broad s), 7.18-7.33(5H, m); IR(NaCl/neat)υ: 3358, 3062, 3029, 3004, 2977, 2952, 2933, 1724, 1497, 1367, 1333, 1249, 1214, 1160, 1059 cm^{-1}; $[\alpha]_D^{25}$ = + 74.8 ° (c = 1.10, CH_2Cl_2) ; HRMS(FAB)calcd for $C_{16}H_{21}NO4$ ($[M+H]^+$)292.1549; obsd($[M+H]^+$)292.1561.

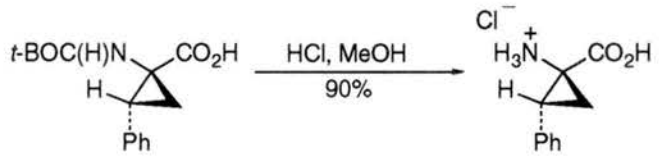


146 **147**

(1S,2R)-1-(N-(*tert*-Butoxycarbonyl)amino-2-phenylcyclopropane-1-carboxylic acid (147).

A mixture of **146** (43.8 mg, 0.15 mmol, 1.0 equiv), $LiOH{\cdot}H_2O$ (63.1 mg, 1.50 mmol, 10.0 equiv), MeOH (4.0 mL), and H_2O (2.0 mL) was refluxed for 2.5h. The reaction was cooled to 0 °C, acidified to pH ≈ 2.5, and the product extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, dried over Na_2SO_4, and filtered. Evaporation of solvent provided 40.4 mg (96.9 %) analytically pure **147** as a clear oil.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.47(9H, s), 1.57(1H, broad s), 2.14(1H, broad s), 2.82(1H, apparent t, J = 9.1 Hz), 5.33(1H, broad s, amide), 7.19-7.28(5H, m); IR(NaCl/neat)υ: 3559-2205(broad), 3313, 3248, 3091, 3063, 3029, 2981, 2933, 2718, 2598, 1706 (broad), 1497, 1453, 1393, 1368, 1251, 1221, 1164, 1063 cm^{-1}; $[\alpha]_D^{25}$ = +86.5 ° (c = 1.32, CH_2Cl_2); HRMS(FAB)calcd for $C_{15}H_{19}NO_4$ ($[M+H]^+$) 278.1392; obsd ($[M+H]^+$)278.1389.

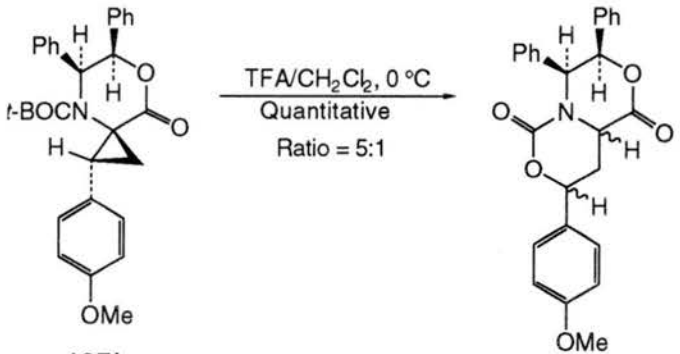


147 **142·HCl**

(1S,2R)-(+)-2-Phenyl-1-amino-1-cyclopropane-1-carboxylic acid (142·HCl).

A -15 °C solution of anhydrous 1N HCl in MeOH (5.1 mL, 5.05 mmol, 40 equiv) was added to **147** as a neat oil and the resulting mixture stirred for 4 h at -15 °C and 1h at room temperature. The reaction was concentrated to dryness and the crude amino acid hydrochloride salt was purified by aqueous elution on a C_{18} reverse phase Sep-pak cartridge, providing 21.1 mg (78.2 %) **142·HCl** as a white crystalline solid.

^{1}H NMR(300 MHz)(D_2O)δHOD at 4.64: 1.75(1H, dd, J_{gem} = 10.0 Hz, J_{vic} = 2.7 Hz), 2.01(1H, apparent t, J = 7.8 Hz), 2.98(1H, apparent t, J = 9.5 Hz), 7.20(5H, s); IR(KBr)υ: 3665-2000 (broad), 3435, 3004, 1712, 1594, 1498, 1267, 1183 cm^{-1}; $[\alpha]_D^{25}$(obsd) = + 72.7 ° (c = 1.0, H_2O); $[\alpha]_D^{25}$(lit)[15f] = + 74.4 ° (c = 1.0, H_2O).

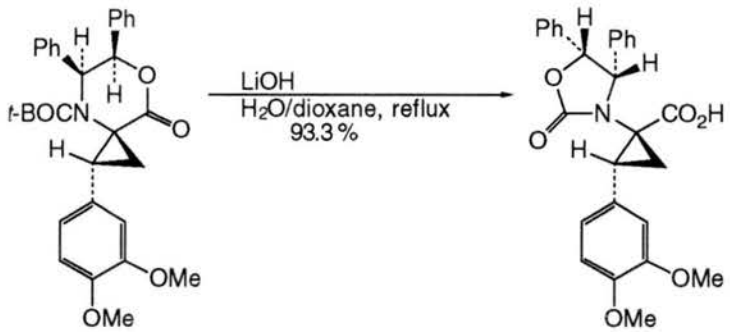


127h **152**

Bicyclic urethane (152).

To a 0 °C solution containing **127h** (101.0 mg, 0.21 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added TFA (320.5 μL, 4.16 mmol, 20 equiv). The reaction immediately turned bright orange and was stirred at 0 °C for 4h. The solvent and excess TFA were evaporated completely and the crude solid was redissolved in CH_2Cl_2 (5 mL) followed by the addition of Et_3N (1.0 mL). The resulting mixture was washed thoroughly with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification via crystallization from CH_2Cl_2 provided 80.1 mg (99.9%) bicyclic urethane **152** as a 5:1 mixture of diastereomers (fine white needles).

^1H NMR(300 MHz)($CDCl_3$)δTMS: 2.51- 2.63(1H, m), 2.87-2.93(1H, m), 3.83(s) and 3.85(s)(3H), 4.48(dd, J_{gem} = 9.6 Hz, J_{vic} = 4.8 Hz) and 4.90(dd, J_{gem} = 11.1 Hz, J_{vic} = 7.5 Hz)(1H), 5.33(d, J = 3.2 Hz) and 5.37(d, J = 2.8 Hz)(1H), 5.48(dd, J_{gem} = 12.0 Hz, J_{vic} = 10.1 Hz) and 5.69(apparent t, J = 3.8 Hz)(1H), 5.84(d, J = 3.0 Hz) and 6.02(d, J = 3.0 Hz)(1H), 6.65-6.70(2H, m), 6.91-7.00(5H, m), 7.10-7.37(7H, m); IR(KBr)υ: 3065, 3031, 3010, 2937, 2910, 2839, 1754, 1703, 1409, 1352, 1263, 1234, 1180, 1051 cm^{-1}; $[\alpha]_D^{25}$ = -141.6 °(c = 0.84, CH_2Cl_2); mp = 276-278 °C. Anal.(recrystallized from CH_2Cl_2). Calcd for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26. Found: C, 72.86; H, 5.57; N, 3.26.



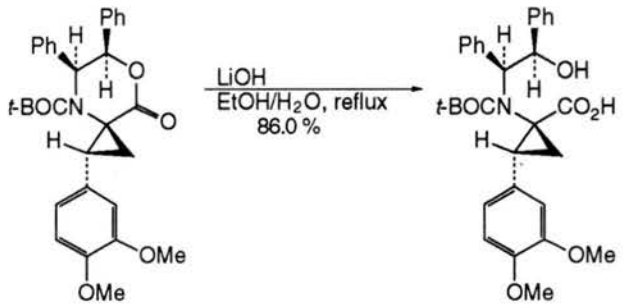
127i **156**

Cyclic urethane (156).

A mixture containing **127i** (77.0 mg, 0.15 mmol, 1.0 equiv), $LiOH{\cdot}H_2O$ (62.7 mg, 1.49 mmol, 10.0 equiv), dioxane (5 mL), and H_2O (5 mL) was refluxed for 1.5 h. The mixture was then cooled and concentrated to dryness. The crude residue was redissolved in H_2O (5 mL) and acidified with 2M HCl (aq) until a heavy white precipitate

formed. The product was extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated providing 64.0 mg (93.3%) cyclic urethane (**156**) as a clear oil. No further purification was necessary.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.99(1H, dd, J_{gem} = 9.6 Hz, J_{vic} = 3.6 Hz), 2.22(1H, dd, J_{gem} = 9.0 Hz, J_{vic} = 2.7 Hz), 2.62(1H, apparent t, J = 9.3 Hz), 3.75(3H, s), 3.82(3H, s), 5.46(1H, d, J = 8.8 Hz), 6.03(1H, d, J = 8.7 Hz), 6.37(1H, broad s), 6.48(1H, d, J = 8.0 Hz), 6.68(1H, d, J = 8.3 Hz), 6.99-7.02(4H, m), 7.10-7.26(6H, m); IR(KBr)υ: 3559-2360 (broad), 3064, 3036, 3008, 2959, 2936, 2913, 2836, 1762 (broad), 1518, 1456, 1417, 1365, 1255, 1235, 1159, 1140, 1027 cm^{-1}.



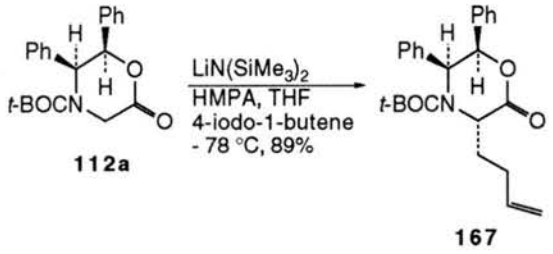
127i **154**

(1S,2R,1'S,2'R)-1-(N-(*tert*-butoxycarbonyl)-N-(1',2'-diphenyl-2'-hydroxyethyl)amino)-2-(3'',4''-dimethoxyphenyl)-cyclopropane-1-carboxylic acid (154).

A slurry of **127i** (50.0 mg, 0.10 mmol, 1.0 equiv), LiOH·H_2O (4.5 mg, 0.11 mmol, 1.1 equiv), EtOH (3 mL), and H_2O (1 mL) was refluxed gently until the mixture became homogeneous (~ 15 min). The reaction was cooled to 0 °C and acidified to pH 2.0 using 2.0 M HCl. The product was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated to a clear oil. Purification via preparative thin layer chromatography (98:1:1, CH_2Cl_2/MeOH/CH_3CO_2H) provided 44.5 mg (86.0%) **154** as a white crystalline solid and 4.6 mg (9.2%) unreacted **127i**.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 1.50(1H, dd, J_{gem} = 10.1 Hz, J_{vic} = 4.2 Hz), 1.56(9H, s), 2.28(1H, dd, J_{gem} = 8.7 Hz, J_{vic} = 2.8 Hz), 2.65(1H, apparent t, J = 9.4 Hz), 3.73(3H, s), 3.78(1H, d, J = 4.9 Hz), 3.81(3H, s), 4.86(1H, s), 5.76(1H, s), 5.84(1H, broad s), 6.54-6.61(2H, m), 6.71(1H, d, J = 8.2 Hz), 6.87-6.90(2H, m), 7.17-7.30(8H, m); IR(KBr)υ: 3386, 2345, 3090, 3064, 3008, 2982, 2973, 2947, 2930, 1726,

1676, 1519, 1418, 1348, 1329, 1234, 1172, 1141, 1024 cm^{-1}; $[\alpha]_D^{25}$ = + 80.2 ° (c = 0.86, CH_2Cl_2); mp = 194-195 °C (dec). Anal.(recrystallized from EtOAc). Calcd for $C_{31}H_{35}NO_7$: C, 69.78; H, 6.61; N, 2.62. Found: C,69.90; H, 6.56; N, 2.60.



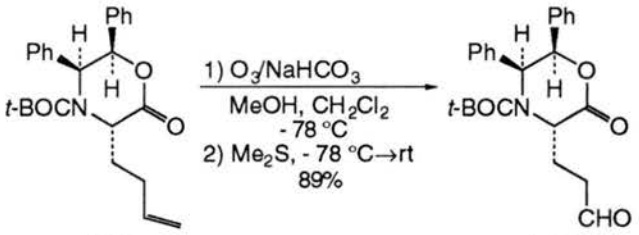
112a **167**

(3S,5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-(3'-butenyl)2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (167).

To a -78 °C mixture of lactone **112a** (1.0 g, 2.83 mmol, 1.0 equiv), 4-iodo-1-butene (1.54 g, 8.49 mmol, 3.0 equiv), HMPA (492.3 mL, 2.83 mmol, 1.0 equiv), and THF (10 mL) was added 1.0 M lithium bis(trimethylsilyl)amide in THF (3.11mL, 3.11 mmol, 1.1 equiv). The reaction was slowly warmed to room temperature and stirred overnight. The mixture was quenched with saturated NaCl (aq) and extracted with 3 x 5 mL EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash silica chromatography (87 g silica, 1:10 EtOAc/hexanes) provided 1.03 g (89.2 %) **167** as a clear glassy solid.

^1H NMR (300 MHz)(DMSO-d_6/K)δTMS: 1.18(9H, s), 2.14-2.34(4H, m), 4.81(1H, apparent t, J = 6.9 Hz), 5.02-5.18(3H, m), 5.85-5.98(1H, m), 6.17(1H, d, J = 3.2 Hz), 6.55-6.58(2H, m), 7.04-7.27(8H, m); IR(KBr)υ: 3072, 3031, 3007, 2981, 2932, 1752, 1699, 1638, 1397, 1272, 1176, 1056 cm^{-1}; $[\alpha]^{25}_D$ = - 54.6 ° (c = 1.0, CH_2Cl_2); mp = 152-153 °C; Anal.(recrystallized from EtOH) Calc'd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.43; H, 7.13; N, 3.22.

(3R,5R,6S)-167: Yield (from **112b**) = 68.1%; $[\alpha]^{25}_D$ = + 57.2° (c = 1.0, CH_2Cl_2); mp = 149-151°C (from EtOH).



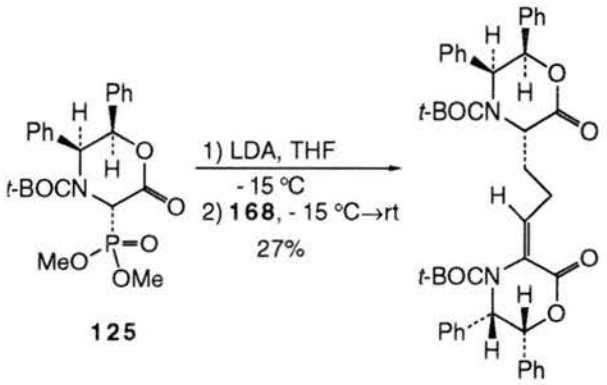
167 **168**

(3S,5S,6R)-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-3-(2'-carbonylethyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (168).

To a -78 °C slurry of **167** (614 mg, 1.51 mmol, 1.0 equiv), $NaHCO_3$ (1.27 g, 15.07 mmol, 10.0 equiv), and 5:1 CH_2Cl_2/MeOH (60 mL) was bubbled excess O_3 until a faint blue color persisted. Excess O_3 was removed by bubbling O_2 through the slurry and the reaction quenched with excess Me_2S at - 78 °C. The mixture was warmed to room temperature and stirred overnight, filtered, and concentrated. Flash silica chromatography (31 g silica, 1:5 EtOAc/hexanes) provided 548.6 mg (88.9 %) **168** as a white powder.

^{1}H NMR (300 MHz)(DMSO-d_6/373 K)δTMS: 1.17(9H, s), 2.29-2.43(2H, m), 2.66-2.75(2H, m), 2.81-2.91(2H, m), 4.82(1H, apparent t, J = 7.7 Hz), 5.14(1H, d, J = 3.0 Hz), 6.20(1H, d, J = 3.2 Hz), 6.55-6.57(2H, m), 7.03-7.25(8H, m), 9.74(1H, apparent t, J = 1.3 Hz); IR(KBr)υ: 3069, 3032, 2977, 2936, 2819, 2722, 1750, 1726, 1695, 1454, 1393, 1272, 1168, 1051 cm^{-1}; $[\alpha]^{25}_D$ = -51.3 ° (c = 1.0, CH_2Cl_2); mp = 160-162 °C; Anal. Calc'd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.38; H, 6.71; N, 3.43.

(3R,5R,6S)-168: Yield (from **(3R,5R,6S)-167**) = 84.3%; $[\alpha]^{25}_D$ = +51.6° (c = 1.0, CH_2Cl_2); mp = 164-166 °C.



125

(E)-(5S,6R,3'S,5'S,6'R)-169

(E)-(5S,6R,3'S,5'S,6'R)-alkene (169).

To a -15 °C solution of phosphonate ester **125** (1.35 g, mmol, 2.0 equiv) in THF (5 mL) was added 7.3 mL of 0.4 M LDA in THF (2.93 mmol, 2.0 equiv) via cannula. The mixture was stirred for 1h and **168** (599.0 mg, 1.46 mmol, 1.0 equiv) was added in a single heap. The reaction was slowly warmed to room temperature, stirred for 1 day, and quenched with saturated NaCl (aq). The product was extracted with 3 x 5 mL EtOAc, dried over $MgSO_4$, filtered, and concentrated. Flash silica chromatography (45 g silica, 1:5 EtOAc/hexanes) followed by washing with hot EtOH provided 298.2 mg (27.4%, 38.3% based on recovered **125**) **169** as a white powder.

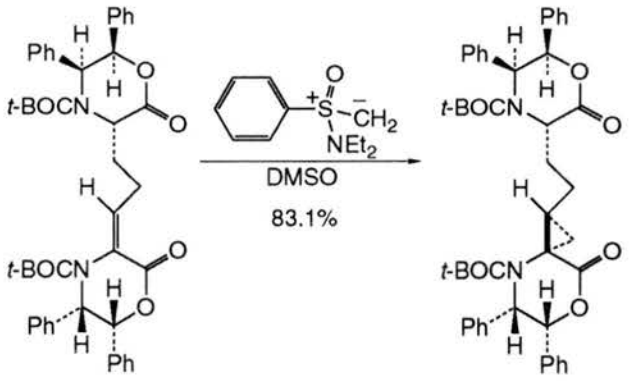
^{1}H NMR (300 MHz)(DMSO-d_6/373 K)δTMS: 1.18(18H, s), 2.34-2.41(2H, m), 2.69-2.80(2H, m), 4.90(1H, apparent t, J = 7.8 Hz), 5.20(1H, d, J = 2.9 Hz), 5.33(1H, d, J = 2.9 Hz), 6.00(1H, d, J = 2.9 Hz), 6.23(1H, d, J = 3.2 Hz), 6.58(2H, d, J = 6.7 Hz), 6.67(2H, d, J = 6.7 Hz), 6.72(1H, apparent t, J = 7.8 Hz), 7.04-7.24(16H, m); IR(KBr)u: 3067, 3033, 2977, 2929, 1751, 1702, 1655, 1389, 1369, 1354, 1313, 1165 cm^{-1}; $[\alpha]^{25}_D$ = -73.2 °(c = 1.0, CH_2Cl_2); mp = 233-235 °C (dec); Anal.(recrystallized from EtOH/THF) Calc'd for $C_{45}H_{48}N_2O_8$: C, 72.56; H, 6.49; N, 3.76. Found: C, 72.36; H, 6.59; N, 3.67.

(E)-(5R,6S,3'S,5'S,6'R)-169. Yield (from **(3R,5R,6S)-125** and **(3S,5S,6R)-168**) = 18.6%:

$[\alpha]^{25}_D$ = + 46.0 ° (c = 1.0, CH_2Cl_2); mp = 229-231 °C (dec.); Anal. (recrystallized from EtOAc/hexanes). Calcd for $C_{45}H_{48}N_2O_8$: C, 72.56; H, 6.49; N, 3.76. Found: C, 72.70; H, 6.50; N, 3.77.

(E)-(5S,6R,3'R,5'R,6'S)-169. Yield (from **(3S,5S,6R)-125** and **(3R,5R,6S)-168**) = 32.3%:

^{1}H NMR (300MHz)(DMSO-d_6/373 K)δTMS: 1.16-1.25(20H, m), 2.28-2.38(2H, m), 4.86-4.91(1H, m), 5.17(1H, d, J = 3.0Hz), 5.33(1H, d, J = 3.2 Hz), 6.01(1H, d, J = 2.8 Hz), 6.21(1H, d, J = 3.1 Hz); IR(KBr)υ: 3090, 3064, 3032, 2976, 2932, 1747, 1708, 1702, 1655, 1456, 1386, 1355, 1281, 1259, 1167, 1142, 1115, 1082, 1058 cm^{-1}; $[\alpha]^{25}_D$ = - 45.0 ° (c = 1.0, CH_2Cl_2); mp = 229-231 °C (dec.).



(E)-(5S,6R,3'S,5'S,6'R)-169 **(1S,3S,5S,6R,3'S,5'S,6'R)-170**

(E)-(1S,3S,5S,6R,3'S,5'S,6'R)-Cyclopropane (170).

To a room temperature mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (301.2 mg, 1.01 mmol, 1.5 equiv) and degreased NaH (24.2 mg, 1.01 mmol, 1.5 equiv) was added DMSO (4 mL). After stirring for 0.5 h, the freshly prepared ylide solution was added to a room temperature slurry of **169** (500.0 mg, 0.67 mmol, 1.0 equiv) in DMSO (4 ml). The resulting reaction mixture was stirred for 5 days at room temperature. At this time the reaction was quenched with H_2O (10 mL) and EtOAc (20 mL) was added. The organic layer was thoroughly washed with several portions of H_2O, dried over MgSO4, filtered, and concentrated. Recrystallization of the crude material from absolute EtOH provided 423.3 mg (83.1%) **170** as a white amorphous solid.

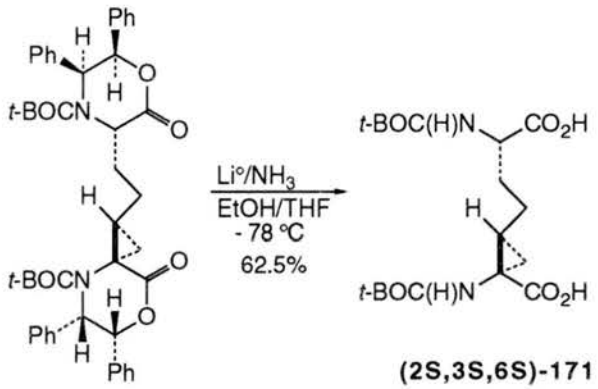
^{1}H NMR(300 MHz)(DMSO-d_6/373 K)δTMS: 1.11(9H, s), 1.16(9H, s), 1.67(1H, dd, J_{gem} = 8.5 Hz, J_{vic} = 2.6 Hz), 1.92(1H, m), 2.07(1H, m), 2.23(2H, m), 2.65(1H, dd, J_{gem} = 9.7 Hz, J_{vic} = 4.0 Hz), 4.85(1H, m), 5.14(1H, d, J = 3.4 Hz), 5.33(1H, d, J = 3.4 Hz), 6.13-6.16(2H, m), 6.56(2H, J = 6.7 Hz), 6.75(2H, d, J = 7.7 Hz), 7.00-7.23(16H, m); IR(KBr)υ: 3065, 3035, 2976, 2930, 2863, 1754, 1704, 1455, 1387, 1367, 1283, 1164, 1063 cm^{-1}; $[\alpha]^{25}_D$ = -5.0 ° (c = 1.0, CH_2Cl_2); mp = 225-226 °C (dec); Anal.(recrystallized from EtOH/THF) Calc'd for $C_{46}H_{50}N_2O_8$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.62; H, 6.70; N, 3.61.

(1S,3S,5S,6R,3'R,5'R,6'S)-170. Yield (from **(E)-(5S,6R,3'R,5'R,6'S)-169** and (±)-(diethylamino)phenyloxosulfonium methylide) = 87.7%:

IR(KBr)υ: 3067, 3033, 2978, 2933, 1752, 1702, 1389, 1364, 1356, 1255, 1162, 1094, 1082, 1062 cm^{-1}; $[\alpha]^{25}_D$ = + 54.4 °(c = 1.0, CH_2Cl_2); mp = 209-211 °C (dec.); Anal. (recrystallized from EtOH/THF). Calcd for $C_{46}H_{50}N_2O_8$: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.06; H, 6.75; N, 3.63.

(1R,3R,5R,6S,3'S,5'S,6'R)-170. Yield (from **(E)-(5R,6S,3'S,5'S,6'R)-169** and (±)-(diethylamino)phenyloxosulfonium methylide) = 93.9%:

^1H NMR(300 MHz)(DMSO-d_6/373 K)δTMS: 1.05-1.41(20H, m), 1.68(1H, dd, J_{gem} = 8.5 Hz, J_{vic} = 2.4 Hz), 1.85-2.00(1H, m), 2.20-2.29(2H, m), 2.66(1H, dd, J_{gem} = 9.5 Hz, J_{vic} = 3.4 Hz), 4.84(1H, m), 5.13(1H, apparent s), 5.32(1H, d, J = 3.2 Hz), 6.14-6.17(2H, m), 6.54-6.57(2H, m), 6.72-6.74(2H, m), 7.00-7.24(20H, m); $[\alpha]^{25}_D$ = - 52.4 ° (c = 1.0, CH_2Cl_2); mp = 208-210 °C (dec.).



(1S,3S,5S,6R,3'S,5'S,6'R)-170 **(2S,3S,6S)-171**

(2S,3S,6S)-2,3-methano-2,6-di(N-(*tert*-Butoxycarbonyl)amino)pimelic acid (171).

To a -78 °C slurry containing **170** (423.0 mg, 0.56 mmol, 1.0 equiv), anhydrous EtOH (327.1 uL, 5.57 mmol, 10.0 equiv), THF(20 mL), and NH_3(45 mL) was added Li° pieces (~76 mg) until a persistent blue color was obtained. The resulting mixture was stirred an additional 10 min and then quenched with solid NH_4Cl. The ammonia was completely evaporated and the resulting white residue was dissolved in H_20 (~15 mL) and washed with Et_2O (3 x 5 mL). The aqueous layer was acidified to pH ~ 2.0 and extracted with EtOAc (3 x 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. Purification of the crude product via preparative TLC (95:4:1, CH_2Cl_2:MeOH:CH_3CO_2H) provided 140.2 mg (62.5 %) **171** as a clear oil.

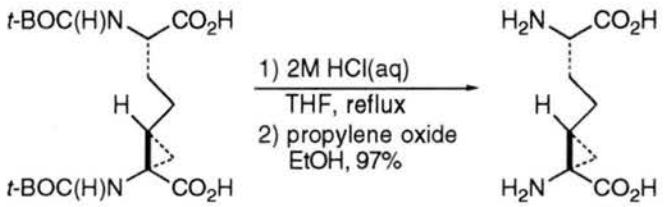
^{1}H NMR (300 MHz)(DMSO-d_6)δTMS: 0.97-1.00(1H, m); 1.15-1.80(24H, m); 3.82-3.92(1H, m); 6.94-7.10(m) and 7.43(s)(2H); 12.29(2H, broad s); IR(NaCl, neat)υ: 3322, 2979, 2934, 2591, 1703(br), 1517, 1395, 1368, 1251, 1165, 1051 cm^{-1}; $[\alpha]^{25}_D$ = +17.80 ° (c = 1.03, CH_2Cl_2); Anal. Calc'd for $C_{18}H_{30}N_2O_8$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.67; H, 7.62; N, 6.95.

(2S,3S,6R)-171. Yield from **(1S,3S,5S,6R,3'R,5'R,6'S)-170** = 64.1%:

IR(NaCl/neat)υ: 3328, 2980, 2935, 2593, 1704, 1515, 1395, 1368, 1253, 1166, 1055 cm^{-1}; $[\alpha]^{25}_D$ = 0.00 ° (c = 1.0, CH_2Cl_2).

(2R,3R,6S)-171. Yield from **(1R,3R,5R,6S,3'S,5'S,6'R)-170** = 59.5%:

$[\alpha]^{25}_D$ = 0.00 ° (c = 1.0, CH_2Cl_2); HRMS(FAB)calcd for $C_{18}H_{30}N_2O_8$ ($[M+H]^+$)403.2080; obsd($[M+H]^+$)403.2078.



171 **163**

(2S,3S,6S)-2,3-Methano-2,6-diaminopimelic acid (163).

To a room temperature solution of **171** (201.0 mg, 0.50 mmol, 1.0 equiv) in THF (15mL) was added 2M HCl (aq) (15 mL). The resulting mixture was refluxed gently for 45 min, cooled to room temperature, and concentrated to dryness. The crude HCl salt was eluted on a Sep-pak C_{18} cartridge with H_2O and concentrated. The HCl salt was then dissolved in absolute EtOH (10 mL) and propylene oxide (~ 5 mL) was added at room temperature. Immediately, the free amino acid precipitated and was collected via Buchner filtration. This was further purified by dissolving the amino acid in H_2O (2 mL) and stirring for 1.5 h with 10 mg decolorizing charcoal. Removal of the charcoal via filtration on Celite and evaporation of solvent provided 98.0 mg (97 %) **163** as a clear glassy solid.

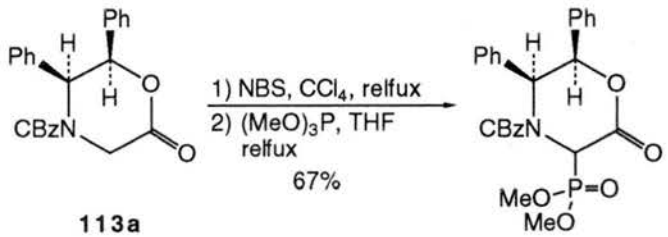
^{1}H NMR (300 MHz)(D_2O)δHOD: 1.27-2.00(7H, m), 3.68(1H, apparent t, J = 5.5 Hz); IR(KBr)υ: 3439, 2989(br), 1627(br), 1509, 1407, 1346 cm^{-1}; $[\alpha]^{25}_D$ = + 10.45° (c = 0.67, H_2O); mp = 210-212 °C (dec).

(2R,3R,6S)-163. Yield from **(2R,3R,6S)-171** = 99.6%:

^{1}H NMR(300 MHz)(D_2O)δHOD: 1.14-1.89(7H, m), 3.56-3.62(1H, m); IR(KBr)υ: 3673-2104 (broad), 1616, 1409, 1349, 1326, 1309, 1236, 1206 cm^{-1}; $[\alpha]^{25}_D$ = - 18.2 ° (c = 0.5, H_2O); mp = 215-217 °C (dec.); Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.33; H, 7.15; N, 13.78.

(2S,3S,6R)-163. Yield from **(2S,3S,6R)-171** = 83.5%:

$[\alpha]^{25}_D$ = + 18.8 ° (c = 0.5, H_2O); mp = 216-218 °C (dec.).



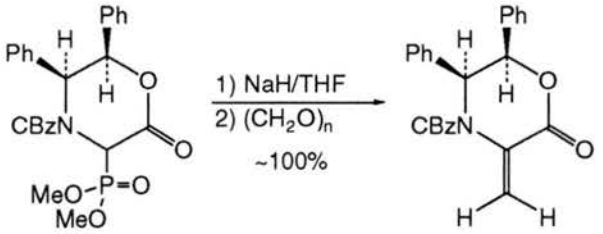
113a **176**

(3S,5S,6R)-4-(Benzyloxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (176).

A mixture of **113a** (3.29 g, 8.49 mmol, 1.0 equiv) and N-bromosuccinimide (1.66 g, 9.34 mmol, 1.1 equiv) in CCl_4 (400 mL) was heated to reflux for 1h, cooled to 0 °C, and filtered through Celite to remove succinimide. After complete removal of solvent, the crude bromide was dissolved in THF (18 mL) and trimethylphosphite (1.1 mL, 9.34 mmol, 1.1 equiv) was added with gentle refluxing for 12 h. After cooling the reaction to room temperature and removing the solvent *in vacuo*, the crude product was purified via flash silica chromatography (80 g silica, 1:1 EtOAc/hexanes) to furnish 2.80 g (66.6%) **176** as a white amorphous solid.

^{1}H NMR (300 MHz)($CDCl_3$)δTMS: 3.60-3.98(6H, m), 4.91(1H, 1/2 ABq, J = 12.3 Hz), 5.01(1H, 1/2 ABq, J = 12.3 Hz), 5.20(d, J = 3.1 Hz) and 5.29(d, J = 3.3 Hz)(1H),

5.48-5.66(1H, m), 6.35(d, J = 3.1 Hz) and 6.40(d, J = 3.1 Hz)(1H), 6.52-7.40(15H, m); IR(NaCl, neat)υ: 3059, 3038, 2857, 1956, 1886, 1760, 1715, 1498, 1453, 1403, 1352, 1297, 1267, 1186, 1111, 1051, 1031 cm^{-1}; Anal.(recrystallized from EtOH) Calc'd for $C_{26}H_{26}NO_7P$: C, 63.03%; H, 5.29%; N, 2.83%. Found: C, 63.17%; H, 5.49%; N, 2.76%; $[\alpha]^{25}_D$ = - 25.5 ° (c = 1.0, CH_2Cl_2); mp = 165-166 °C. The (3R,5R,6S)-isomer has been synthesized in similar fashion: $[\alpha]^{25}_D$ = + 25.2 ° (c = 1.0, CH_2Cl_2); mp = 167-169 °C.

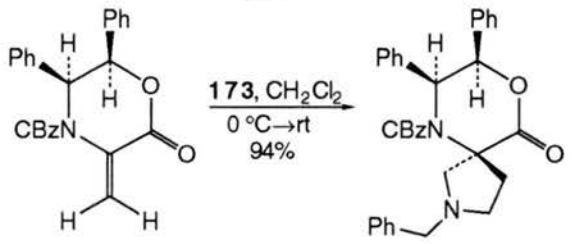


176 **175**

(5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methylidene-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (175).

To a mixture of **176** (900 mg, 1.82 mmol, 1.0 equiv) and degreased NaH (45.8 mg, 1.91 mmol, 1.1 equiv) at room temperature was added THF (5 mL). Within 10 min H_2(g) evolution ceased and paraformaldehyde (57.3 mg, 1.91 mmol, 1.1 equiv) was added in a single heap. The reaction was stirred overnight, quenched with H_2O (5 mL), and extracted with 3 x 5 mL EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated, providing 730 mg (100%) **175** as a white amorphous solid. No further purification is necessary and crude **175** can be carried on to the next reaction.

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 5.04(1H, 1/2 ABq, J = 12.3 Hz), 5.13(1H, 1/2 ABq, J = 12.3 Hz), 5.41(1H, d, J = 2.7 Hz), 5.81(1H, d, J = 2.8 Hz), 6.30(1H, s), 6.52(1H, broad s), 6.66(2H, d, J = 7.4 Hz), 6.99-7.31(13H, m); IR(KBr)υ: 3088, 3061, 3030, 2986, 2939, 2892, 1742, 1718, 1607, 1457, 1395, 1353, 1284, 1272, 1256, 1172, 1086, 1070 cm^{-1}; Anal.(recrystallized from EtOH) Calc'd for $C_{25}H_{21}NO_4$: C, 75.17%; H, 5.30%; N, 3.51%. Found: C, 75.34%; H, 5.54%; N, 3.49%; $[\alpha]^{25}_D$ = - 89.4 ° (c = 1.0, CH_2Cl_2); mp = 152-153.5 °C.

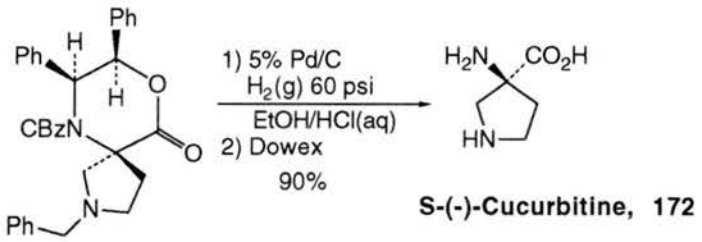


175 **177**

(5S,7S,8R)-2-Benzyl-6-(benzyloxycarbonyl)-7,8-diphenyl-9-oxa-2,6-diazaspiro[4.5]decan-10-one (177).

To a 0 °C solution containing **175** (735.0 mg, 1.84 mmol, 1.0 equiv), N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine (3.1 g, 12.88 mmol, 7.0 equiv), and CH_2Cl_2 (10 mL) was added TFA (28.4 μL, 0.37 mmol, 0.2 equiv) dropwise via syringe. After 15 min the mixture was warmed to room temperature and stirred an additional 3h. Evaporation of solvent and crystallization of the crude product from EtOH provided 916.1 mg (93.5%) **177** as a white amorphous solid.

^{1}H NMR(300 MHz)(373 K, Cl_2DCCl_2) δ TMS: 2.59-2.67 (1H,m); 3.02-3.14 (3H, m); 3.23 (1H, 1/2 ABq, J=9.9 Hz); 3.33 (1H, 1/2 ABq, J = 9.9 Hz); 3.70 (1H, 1/2 ABq, J=13.3 Hz); 3.76 (1H, 1/2 ABq, J = 13.3 Hz); 5.10 (1H, 1/2 ABq, J = 12.5 Hz); 5.16 (1H, 1/2 ABq, J = 12.5 Hz); 5.43 (1H, d, J = 2.8 Hz); 5.68 (1H, d, J = 2.8 Hz); 6.66 (2H, d, J = 7.3 Hz); 7.01-7.32 (18 H, m). IR(KBr)υ: 3087, 3062, 3032, 2938, 2821, 2807, 1744, 1708, 1497, 1455, 1390, 1342, 1277, 1209, 1178, 1127, 1084, 1065cm^{-1}; Anal.(recrystallized from EtOH) Calc'd for $C_{34}H_{32}N_2O_4$: C, 76.67%; H, 6.06%; N, 5.26%. Found: C, 76.82%, H, 6.17%; N, 5.16%; $[\alpha]^{25}_D$ = + 50.5 ° (c = 1.0 CH_2Cl_2); mp = 178-180 °C.

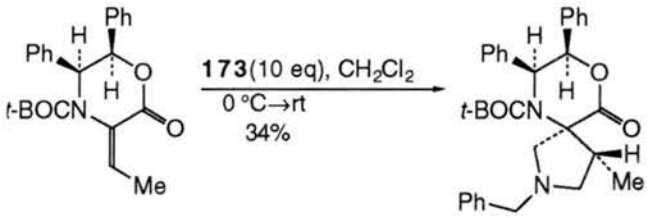


177 **S-(-)-Cucurbitine, 172**

(S)-(-)-Cucurbitine (172).

A mixture of **177** (400.0 mg, 0.75 mmol, 1.0 equiv), 5% Pd/C (160.0 mg, 0.08 mmol, 0.1 equiv), 2M HCl (1.13 mL, 2.25 mmol, 3.0 equiv), and EtOH (20 mL) was thoroughly degassed and pressurized to 60 psi H_2(g) for 12 h. At this time the reaction was again degassed and the catalyst was removed via vacuum filtration using Whatman No. 42 filter paper. The resulting filtrate was concentrated to dryness providing 289.2 mg white solid consisting of bibenzyl and cucurbitine·2HCl. Bibenzyl was removed by triturating the solid mixture with pentane. The crude amino acid was then dissolved in H_2O (~ 1 mL) and sequentially eluted on a C_{18} Sep-Pak cartridge and a small column packed with Dowex® 50x2-400 ion-exchange resin, using H_2O and 0.1M NH_4OH, respectively. Concentration of the fractions collected provided 89.0 mg (90%) **S-(-)-cucurbitine (172)** as a white crystalline solid.

^{1}H NMR(300 MHz)(D_2O)δ(HOD at 4.64 ppm): 1.83-1.93(1H, m), 2.16-2.26(1H, m), 3.02(1H, 1/2 ABq, J = 12.2 Hz), 3.33(2H, apparent t, J = 7.5 Hz), 3.45(1H, 1/2 ABq, J = 12.2 Hz); IR(KBr)υ: 3285, 3061-2380, 2156, 1602, 1388, 1258, 1087, 908 cm $^{-1}$. Anal.(recrystallized from H_2O/EtOH) Calc'd for $C_5H_{10}N_2O_2$: C 46.14; H 7.74; N 21.52. Found: C 46.37; H 7.84; N 21.31 ; $[\alpha]^{25}_D$ = -19.96° (c = 1.02, H_2O); $[\alpha]^{25}_D$ (lit.)[87,88] = - 19.76° (c = 9.31, H_2O) ; mp = 239-241 °C (dec).



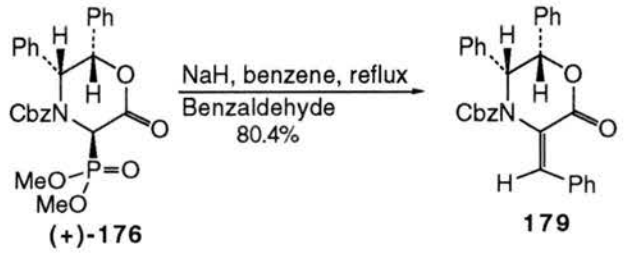
126b **178**

(4S,5S,7S,8R0-2-benzyl-6-(tert-butoxycarbonyl)-7,8-diphenyl-4-methyl-9-oxa-2,6-diazaspiro[4.5]decan-10-one (178):

To a 0 °C solution containing **126b** (100mg, 0.26 mmol, 1.0 equiv), N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine (312.8 mg, 1.32 mmol, 5.0 equiv), and CH_2Cl_2 (2 mL) was added TFA (4.1 μL, 0.05 mmol, 0.2 equiv) dropwise via syringe. After 30 min the mixture was warmed to room temperature and stirred for 4 hours. At this time an additional 5.0 equivalents of amine and 0.2 equivalents of TFA were added to the reaction, since unconsumed **126b** was detected by TLC. The reaction was stirred overnight, concentrated, and the crude product purified by flash silica chromatography

(x 3) (13g-38g silica; 1:10 EtOAc/hexanes) to provide 45.2 mg (33.5%) pyrrolidine **178** as a clear oil:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 0.71(3H, d, J = 6.9 Hz), 1.52(9H, s), 3.02(1H, 1/2 ABq, J = 10.1 Hz), 3.03(1H, apparent t, J = 9.6 Hz), 3.13(1H, apparent t, J = 8.0 Hz), 3.57(1H, m), 3.65(1H, 1/2 ABq, J = 13.3 Hz), 3.79(1H, 1/2 ABq, J = 10.1 Hz), 3.89(1H, 1/2 ABq, J = 13.3 Hz), 5.72(1H, broad s), 5.75(1H, d, J = 2.8 Hz), 7.12-7.38(15, m).

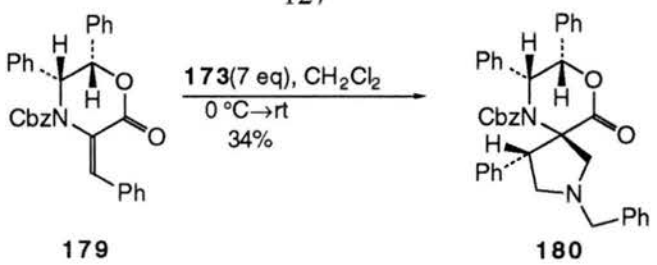


(+)-176 179

(5R,6S)-3-Benzylidene-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (179):

To a room temperature mixture containing **(+)-176** (872.0 mg, 1.76 mmol, 1.0 equiv), degreased NaH (44.4 mg, 1.85 mmol, 1.05 equiv), and benzene (10 mL) was added benzaldehyde (196.8 μL, 1.94 mmol, 1.1 equiv). Immediately the slurry began to evolve H_2 gas and turned homogenous in 0.5 h. The reaction was fitted with a Dean Stark apparatus and the benzene was removed slowly and completely (approximately 1h). The reaction was kept warm for 4h and the crude residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification via crystallization from EtOH provided 673.0 mg (80.4 %) product as fine white needles:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 4.97(1H, 1/2 ABq, J = 12.2 Hz), 5.10(1H, 1/2 ABq, J = 12.3 Hz), 5.35(1H, d, J = 2.8 Hz), 5.91(1H, d, J = 2.8 Hz), 6.70(2H, d, J = 7.5 Hz), 6.91(1H, broad s), 6.97-7.00(2H, m), 7.09-7.39(14H, m), 7.53(2H, d, J = 6.4 Hz); IR(KBr)υ: 3090, 3064, 3031, 2972, 2928, 2894, 1742, 1708, 1655, 1398, 1345, 1274, 1229, 1140 cm^{-1}; $[\alpha]_D^{25}$ = + 132.0 ° (c = 1.0, CH_2Cl_2); mp = 196-198 °C. Anal. (recrystallized from EtOH) Calcd for $C_{31}H_{25}NO_4$: C, 78.30; H, 5.30; N, 2.95. Found: C, 78.10; H, 5.42; N, 2.90.

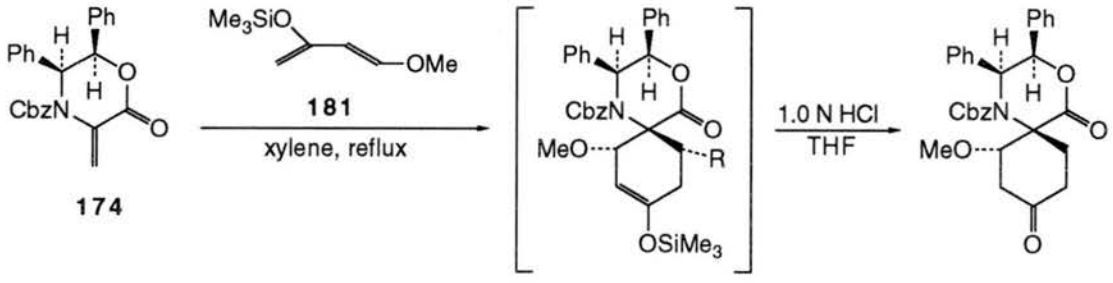


179 180

(4S,5R,7R,8S)-2-Benzyl-6-(benzyloxycarbonyl)-4,7,8-triphenyl-9-oxa-2,6-diazaspiro[4.5]decan-10-one (180):

To a 0 °C solution containing **179** (200 mg, 0.42 mmol, 1.0 equiv), N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine (699.0 mg, 2.94 mmol, 7.0 equiv), and CH_2Cl_2 (2 mL) was added TFA (6.5 μL, 0.08 mmol, 0.2 equiv). The mixture was warmed to room temperature after 15 min and stirred overnight. The reaction was then concentrated to dryness and purified via preparative thin layer chromatography (x 2) (1:1 EtOAc/hexanes and 1:5 EtOAc/hexanes) to provide 87.7 mg (34.3%) pyrrolidine **180** as a white crystalline solid:

^{1}H NMR(300 MHz)($CDCl_3$)δTMS: 3.26(1H, d, J = 10.0 Hz), 3.36(1H, t, J = 8.1 Hz), 3.81-4.06(4H, m), 5.13-5.36(4H, m) 5.63(1H, d, J = 2.9 Hz), 6.23(2H, d, J = 7.1 Hz), 6.69(2H, t, J = 7.7 Hz), 6.90(2H, d, J = 6.6 Hz), 6.98(1H, t, J = 7.4 Hz), 7.05-7.42(18H, m); IR(KBr)υ: 3087, 3063, 3031, 2959, 2847, 1762, 1701, 1497, 1453, 1388, 1337, 1284, 1209, 1176, 1120 cm^{-1}; mp = 94-98 °C; $[\alpha]_D^{25}$ = +54.1° (c = 1.02, CH_2Cl_2); HRMS(EI)calcd for $C_{40}H_{36}N_2O_4$(M^+)608.2675; obsd(M^+)608.2648.



174 182, R = H 184

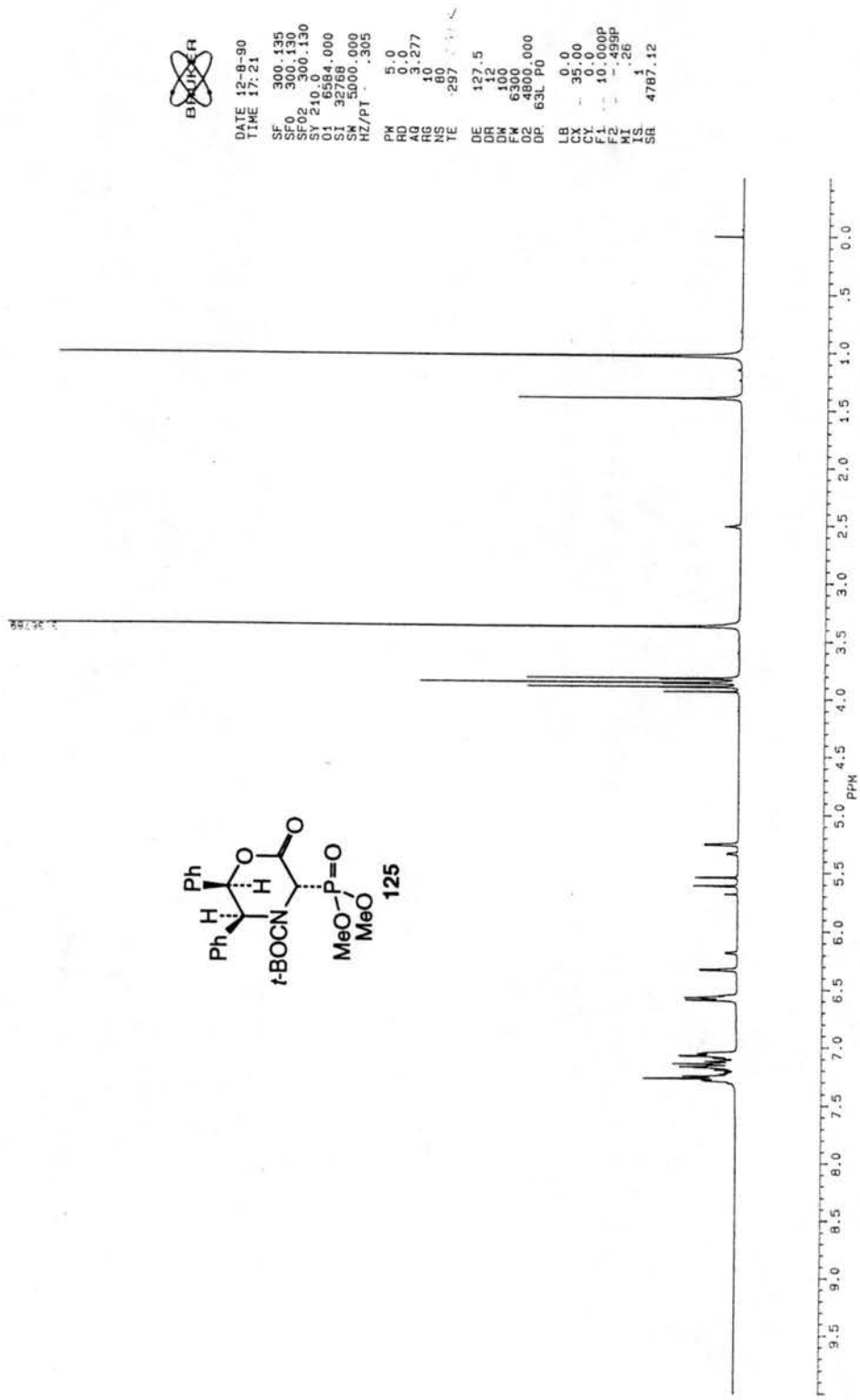
37%, 2 steps

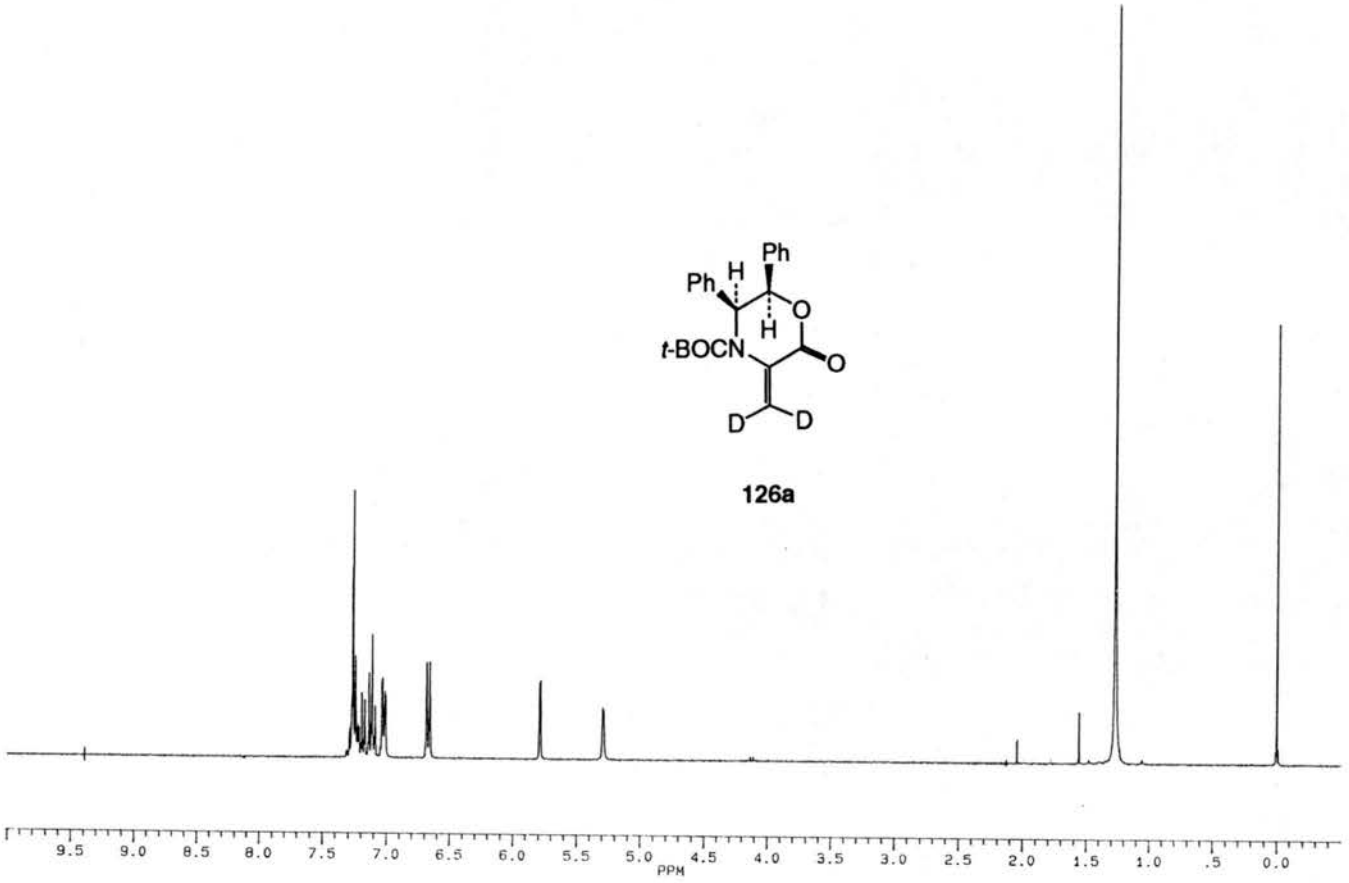
Bicyclo-β-methoxyketone (184).

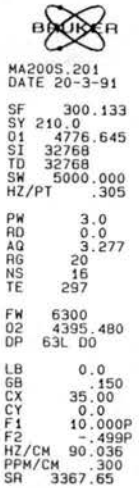
A mixture of **174** (56.0 mg, 0.14 mmol, 1.0 equiv), 1-methoxy-3-trimethylsilyloxy-1,3-butadiene[94] **181** (136.5 μL, 0.70 mmol, 5.0 equiv), and dry xylenes (1mL) was heated to reflux for 6.5 hours. Solvent and excess diene were removed *in vacuo* and the crude product was purified via flash silica chromatography (1:10 EtOAc/hexanes) as a three spot mixture (36.4 mg) containing trimethylsilylenol ether **182** as a crystalline solid. To this mixture was added 1.0 N HCl (aq) (1.0 mL) and THF (1.0 mL) and the resulting solution was stirred for 30 min. At this time, solvent and HCl (aq) were removed *in vacuo* and the crude residue was purified by flash silica chromatography (10g silica, 1:5 EtOAc/hexanes) to provide 26.0 mg (37.1%, two steps) of **184** as a white crystalline solid:

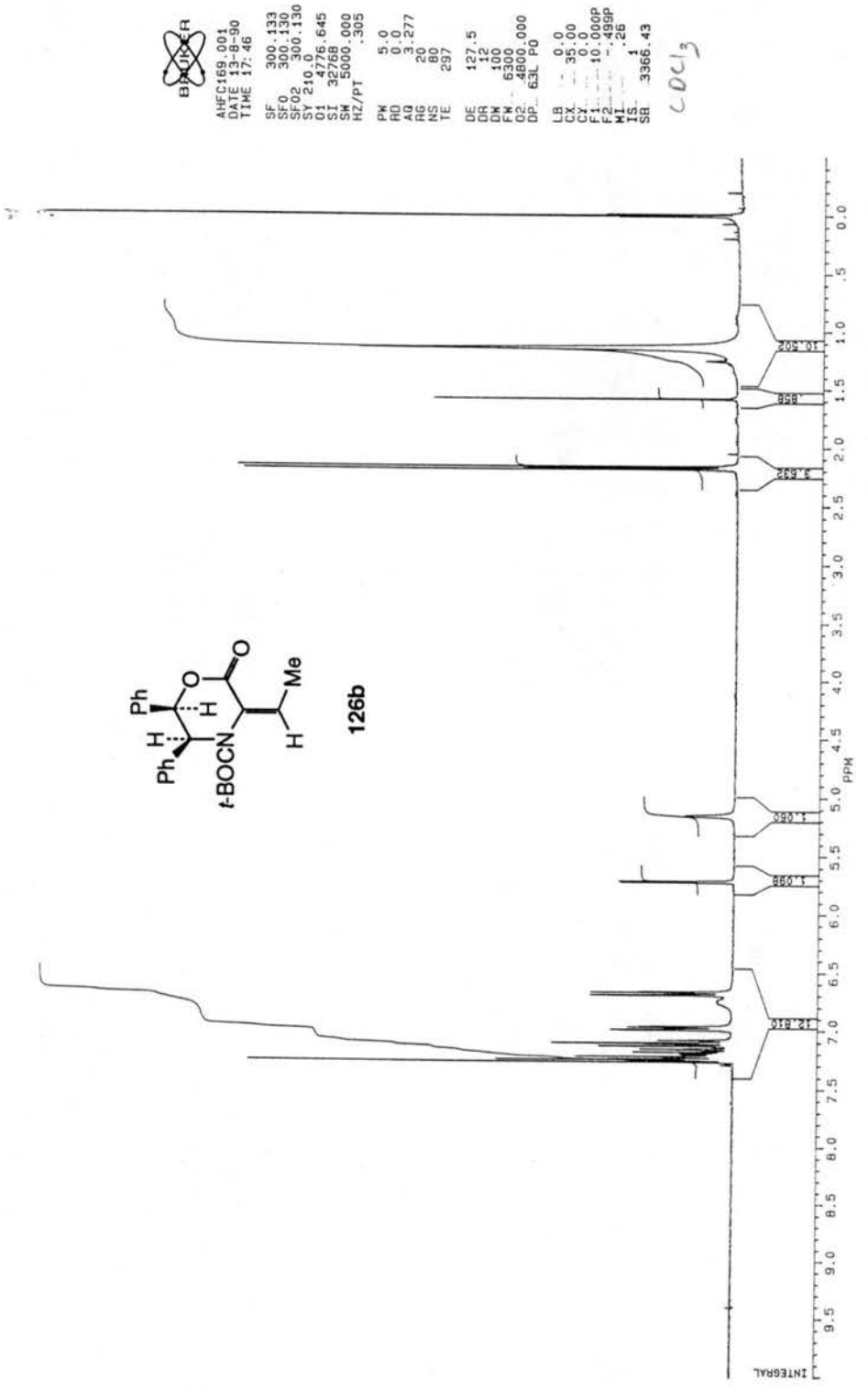
^{1}H NMR(300MHz)($CDCl_3$)δTMS(tentative assignment): 2.55-3.05(6H, m), 3.42(3H, broad s), 5.00-5.30(3H, m), 5.50(1H, broad s), 6.09(d, J = 2.0 Hz) and 6.28(d, J = 2.0 Hz)(1H), 6.92-7.35(15H, m); IR(KBr)υ: 3090, 3065, 3036, 3007, 2967, 2933, 2831, 1745, 1724, 1702, 1396, 1340, 1282, 1215, 1119, 1060 cm^{-1}; $[\alpha]_D^{25}$ = + 83.50 ° (c = 0.50, CH_2Cl_2); mp = 183-185 °C; Anal. Calcd for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80. Found: C, 71.89; H, 5.81; N, 2.60.

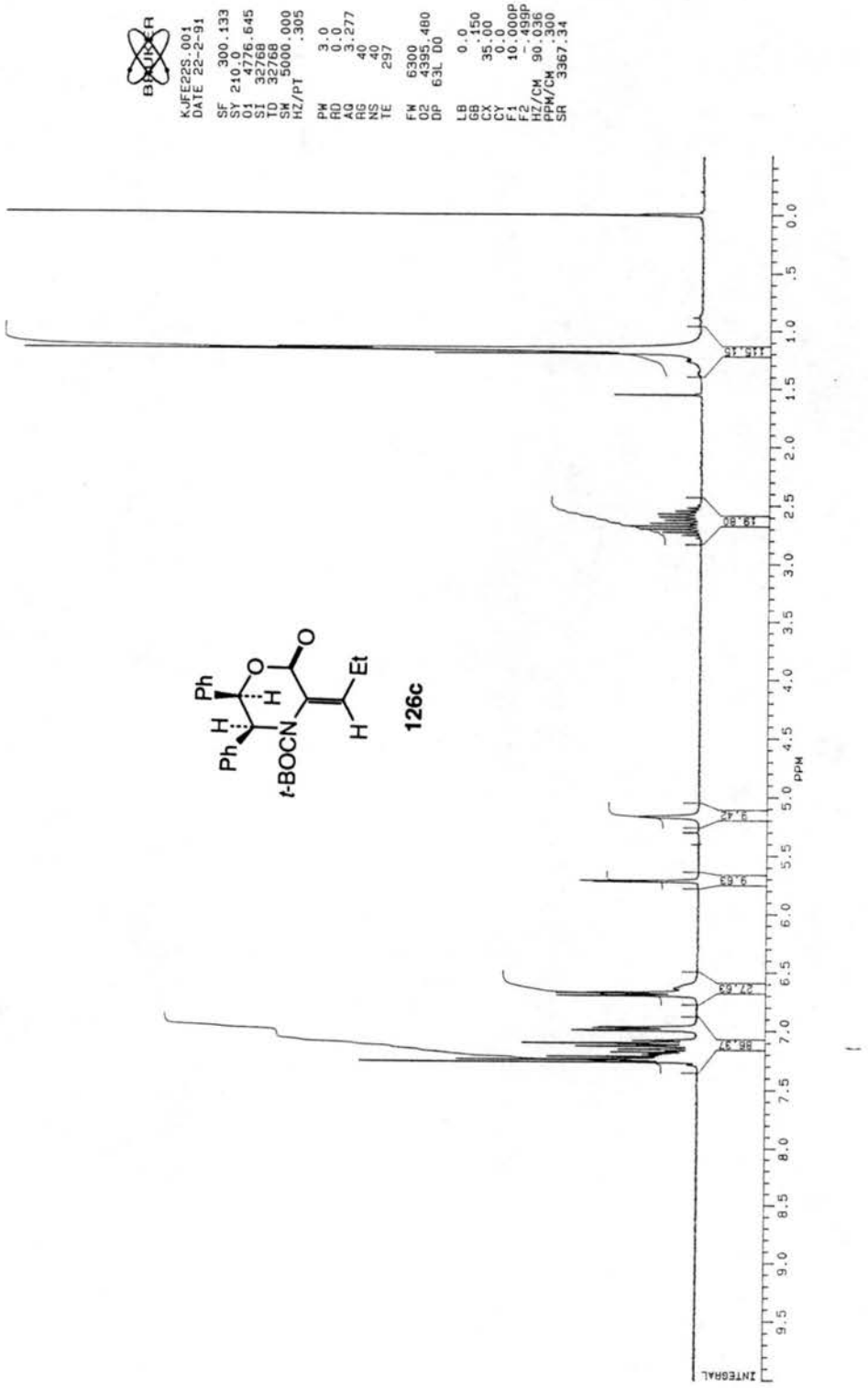
3.2 ^{1}H NMR Spectra

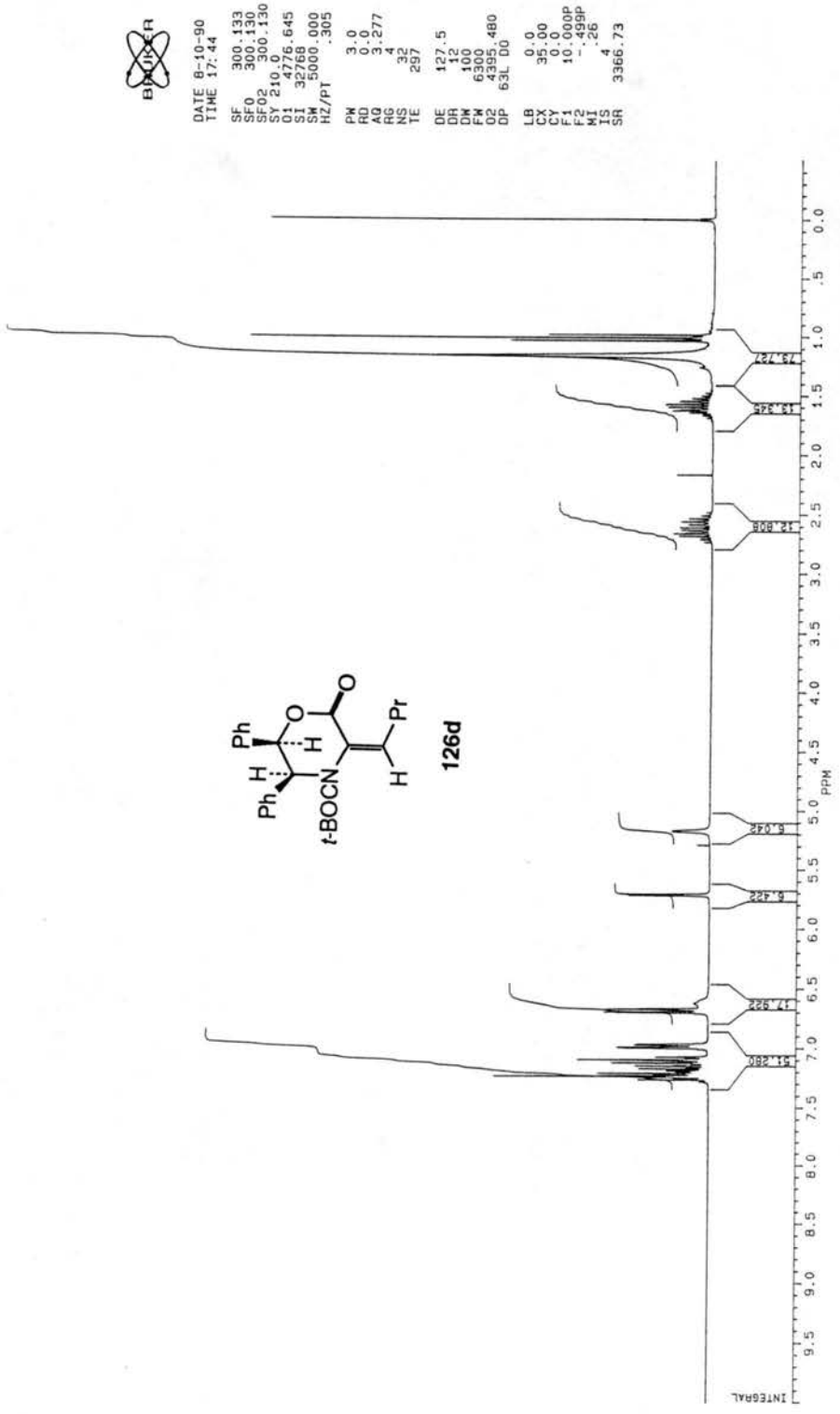


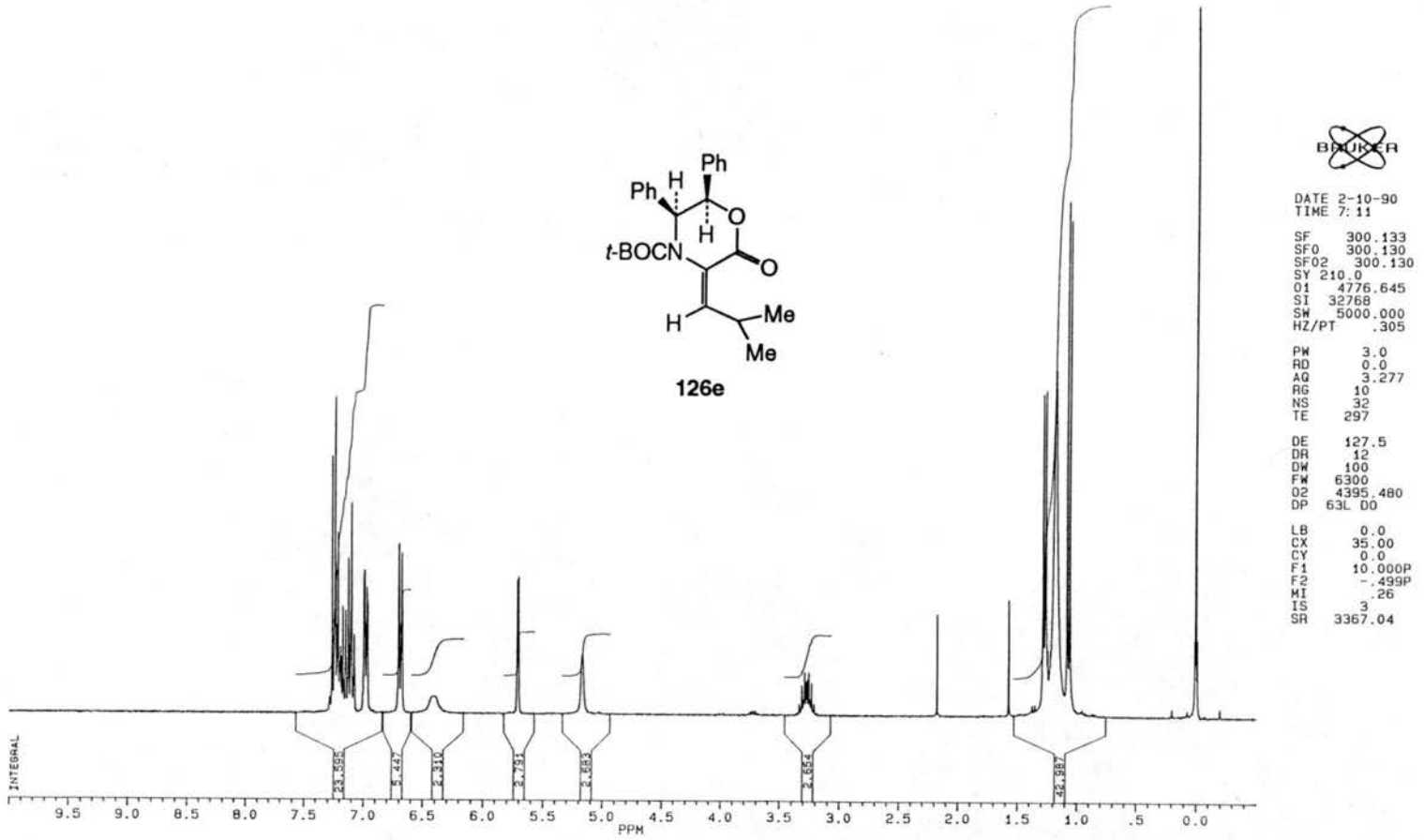

Ph
H
Ph
O
H
t-BOCN
O
D
D
126a
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

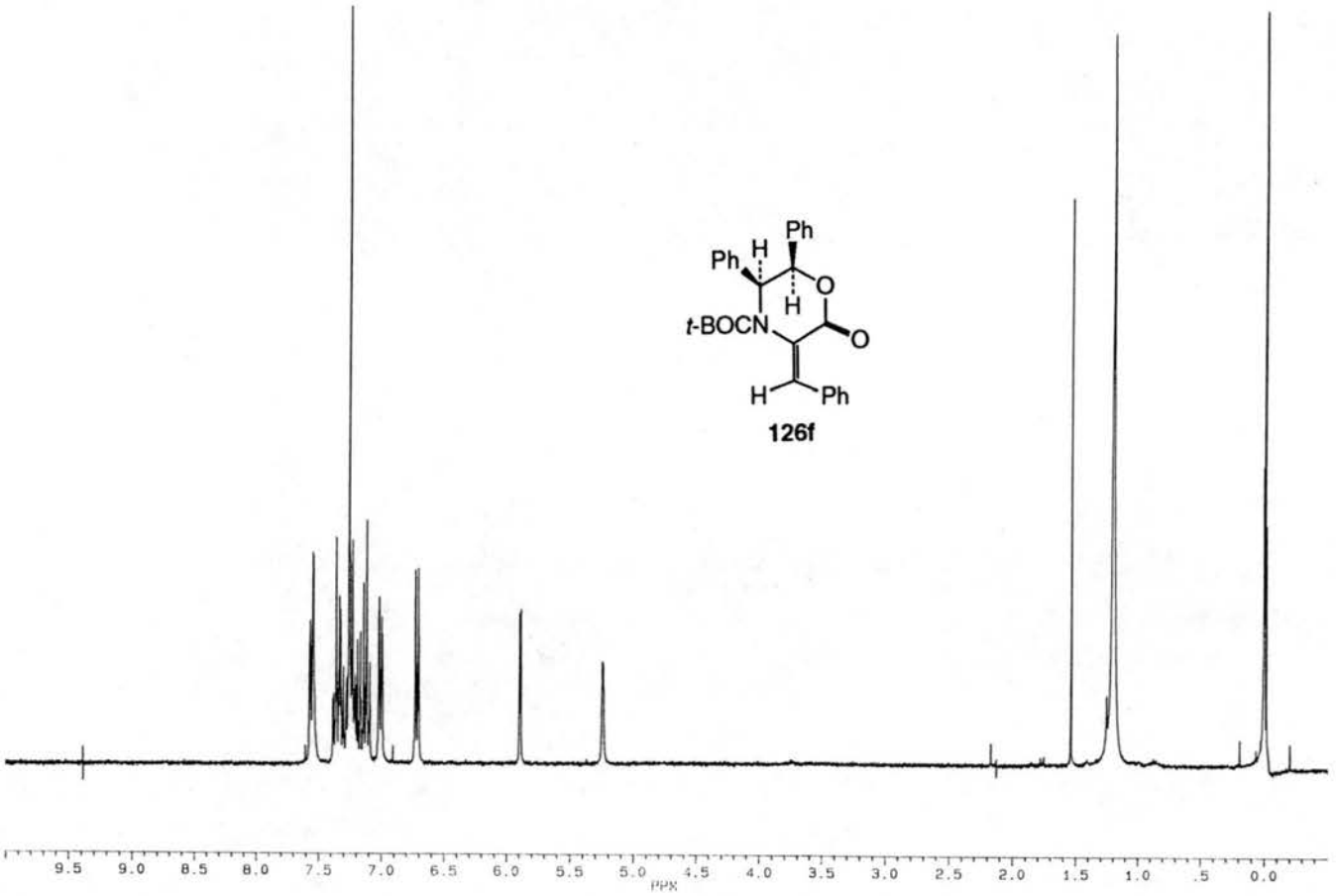

MA200S.201
DATE 20-3-91
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 16
TE 297
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 3367.65

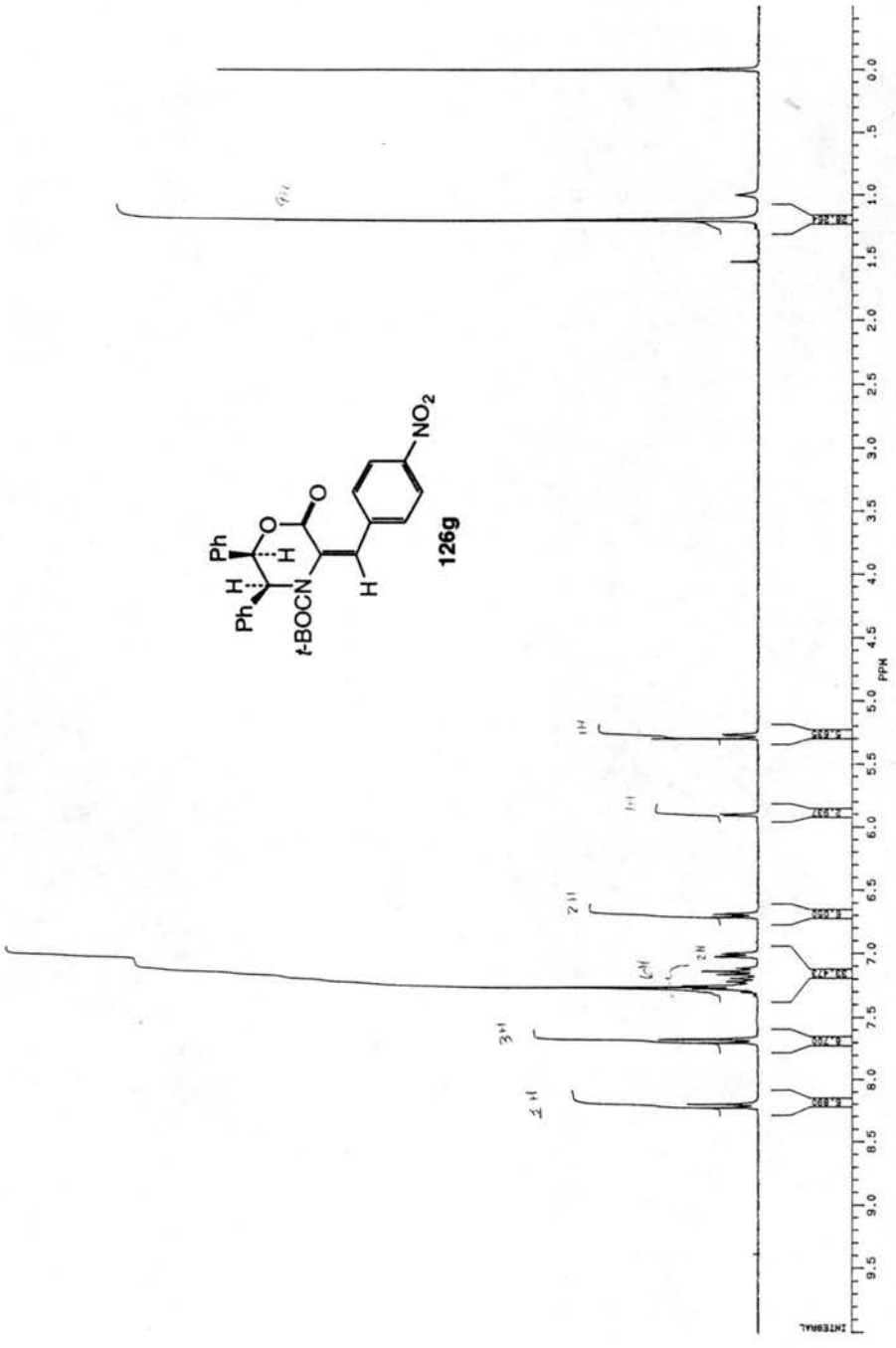

AHFC169.001
DATE 13-8-90
TIME 17:46
SF 300.133
SFO 300.130
SFO2 300.130
SY 210.0
D1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 5.0
RD 0.0
AQ 3.277
RG 20
NS 80
TE 297
DE 127.5
DR 12
DW 100
FW 6300
O2 4800.000
DP 63L PO
LB 0.0
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
MI .26
TS 1
SR 3366.43
CDCl3
10.402
.888
3.682
1.050
1.098
12.810
INTEGRAL
PPM
Ph
H
O
O
H
Ph
t-BOCN
Me
H
126b

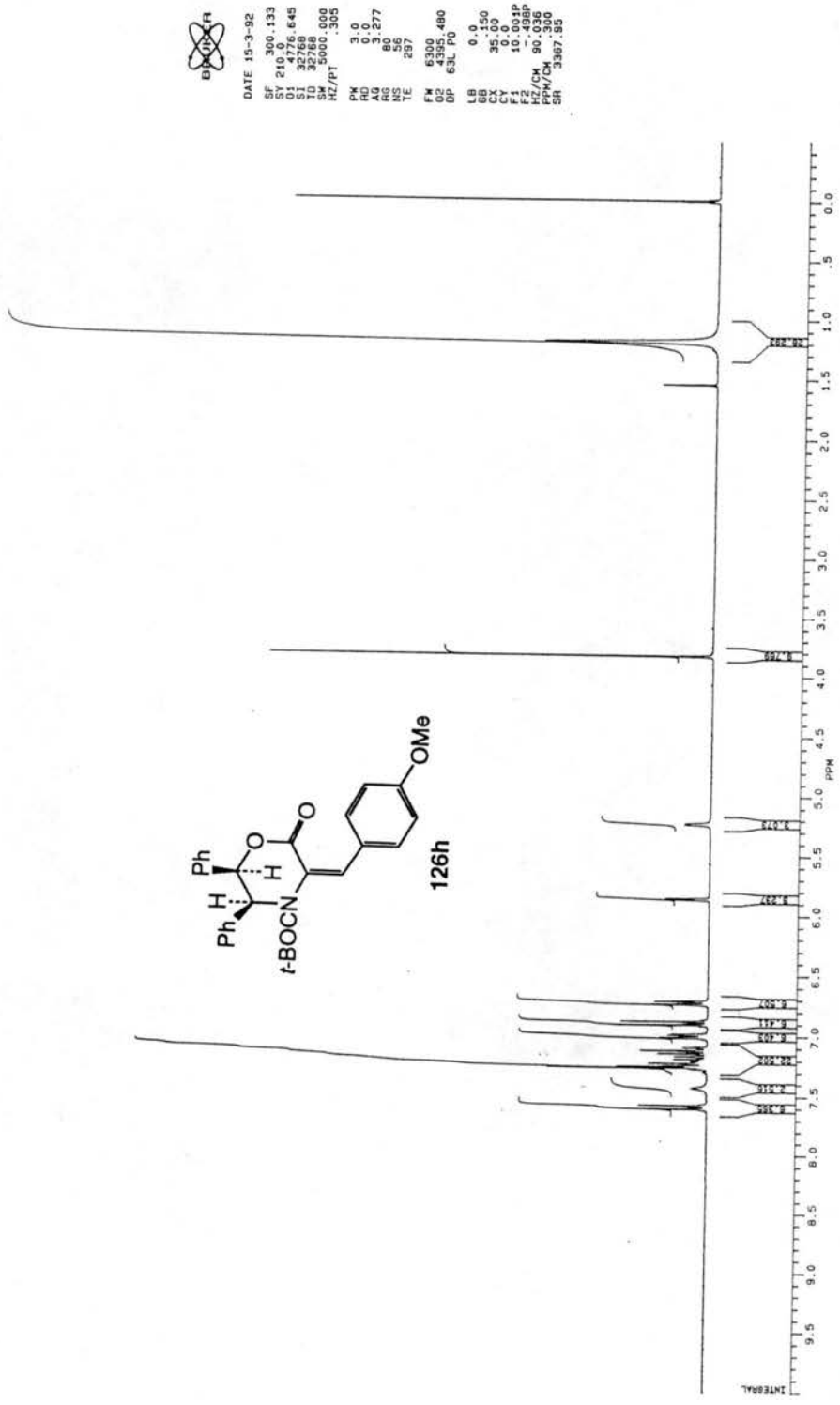

BRUKER
KJFE22S.001
DATE 22-2-91
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 40
NS 40
TE 297
FW 6300
O2 4395.480
DP 63L DO
LB 0.0
GB .150
CX 35.00
CY 0
F1 10.000P
F2 .499P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
Ph
H
O
H
Ph
t-BOCN
Et
H
126c
INTEGRAL
PPM

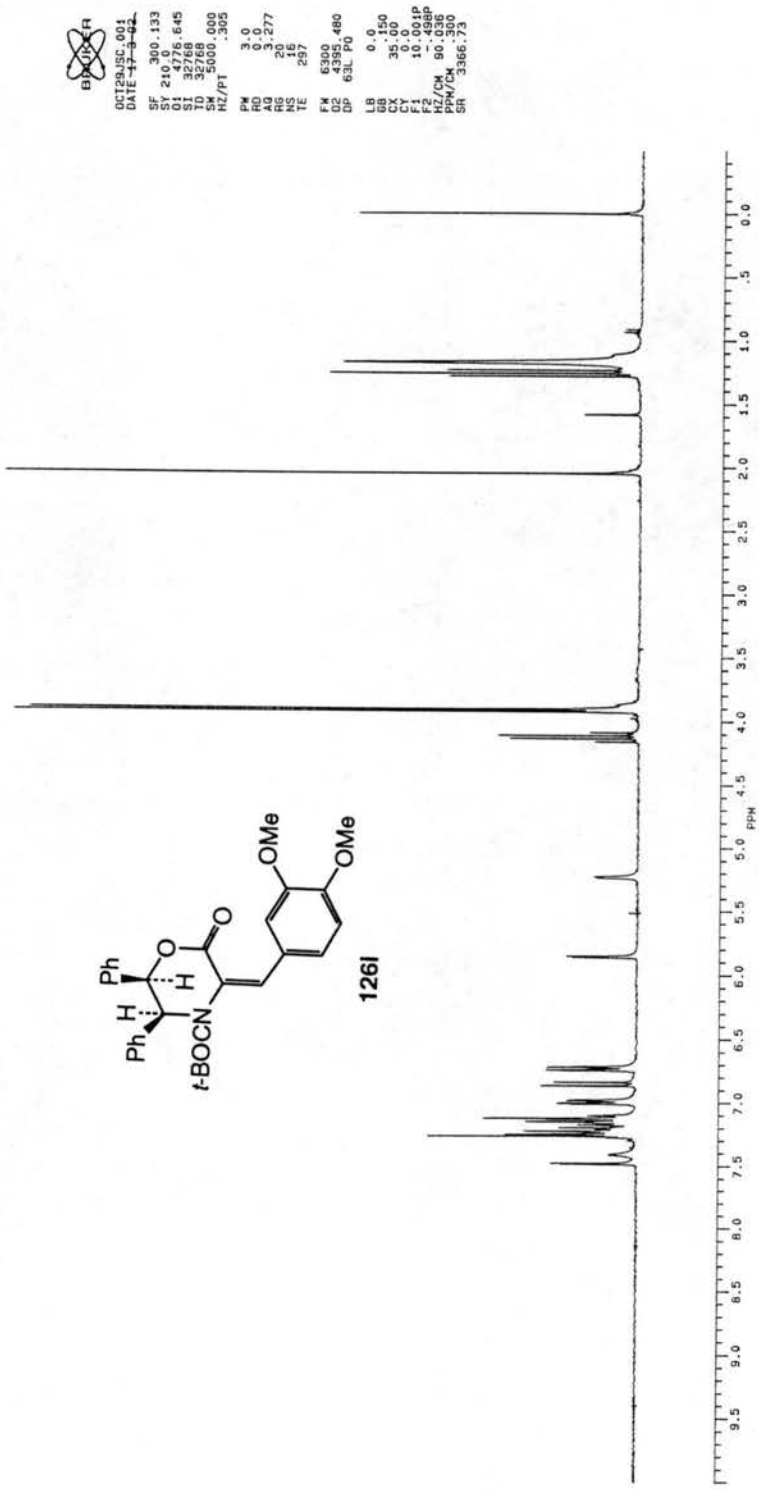

BRUKER
DATE 8-10-90
TIME 17:44
SF 300.133
SFO 300.130
SF02 300.130
SY 210.0
O1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 4
NS 32
TE 297
DE 127.5
DA 12
DW 100
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
MI -.26
IS 4
SR 3366.73
Ph
H
Ph
O
O
H
N
t-BOCN
Pr
H
126d
19.727
19.345
12.808
6.042
6.422
17.922
51.280
PPM
INTEGRAL

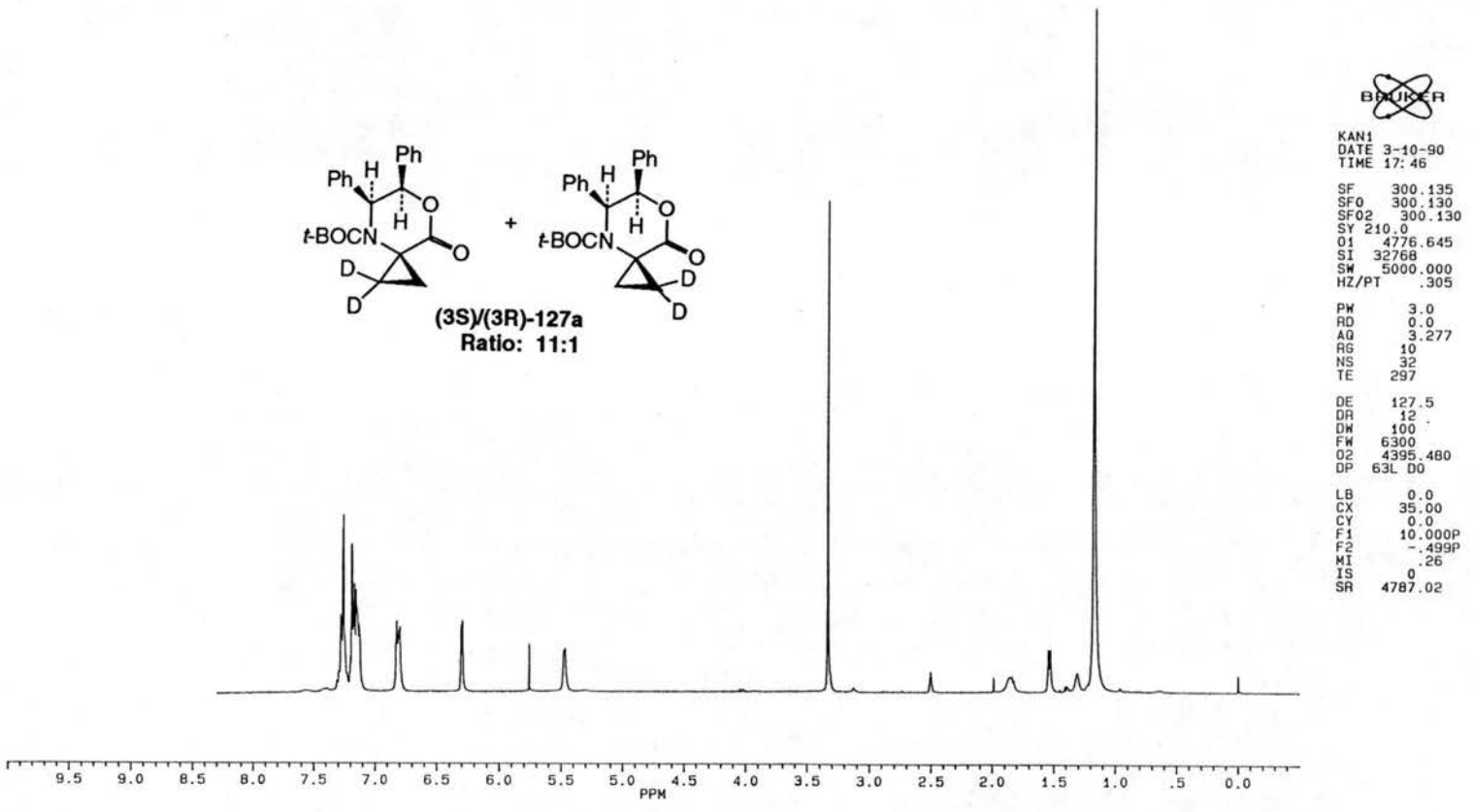

Ph
H
Ph
O
H
t-BOCN
O
H
Me
Me
126e
BRUKER
DATE 2-10-90
TIME 7:11
SF 300.133
SFO 300.130
SF02 300.130
SY 210.0
01 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 10
NS 32
TE 297
DE 127.5
DR 12
DW 100
FW 6300
02 4395.480
DP 63L D0
LB 0.0
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
MI .26
IS 3
SR 3367.04
INTEGRAL
23.595
5.447
2.310
2.791
2.583
2.654
42.287
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

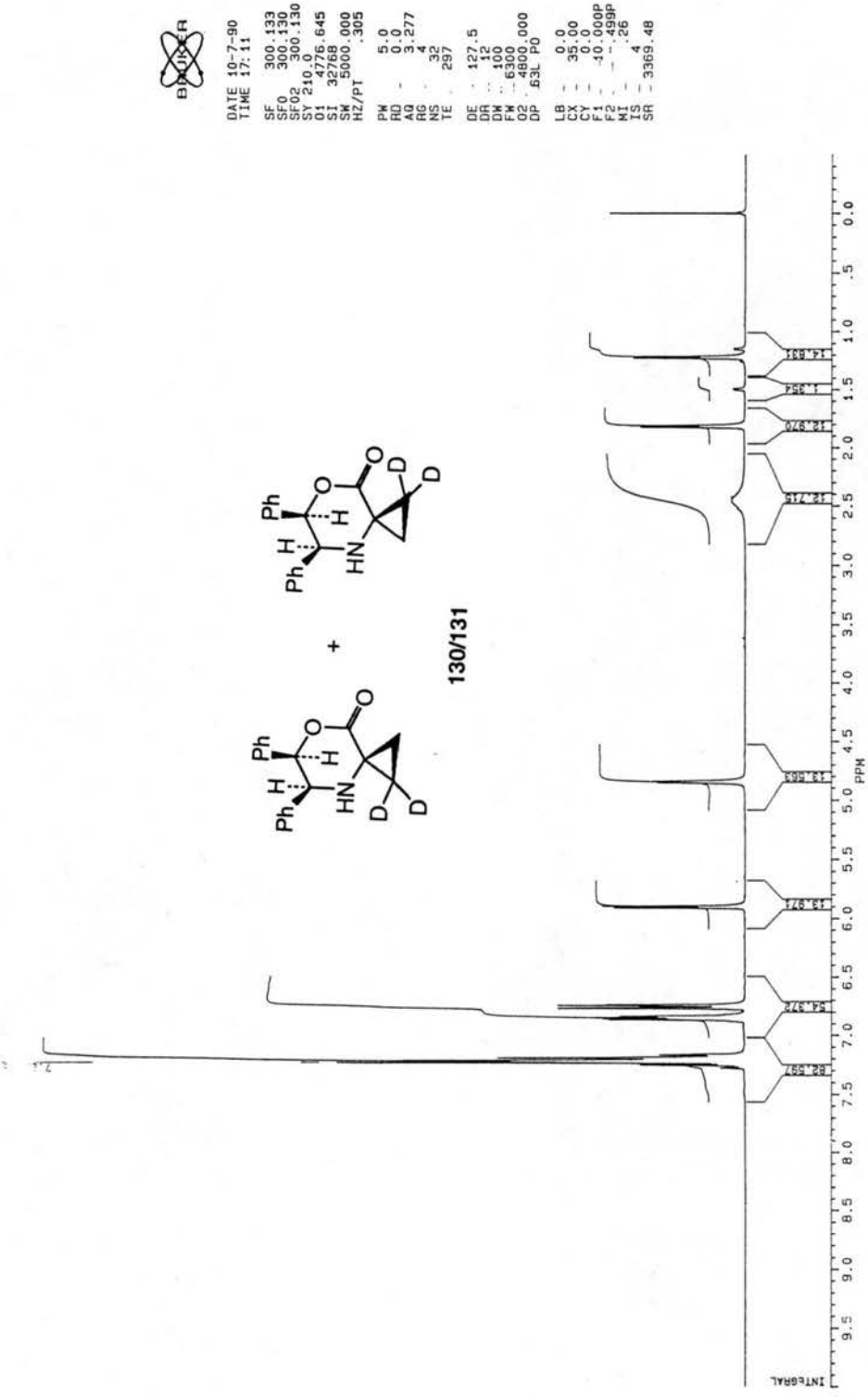

Ph
H
Ph
O
H
t-BOCN
O
H
Ph
126f
BRUKER
DATE 17-1-91
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 100
NS 135
TE 297
FW 6300
O2 4395.480
DP 63L DO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

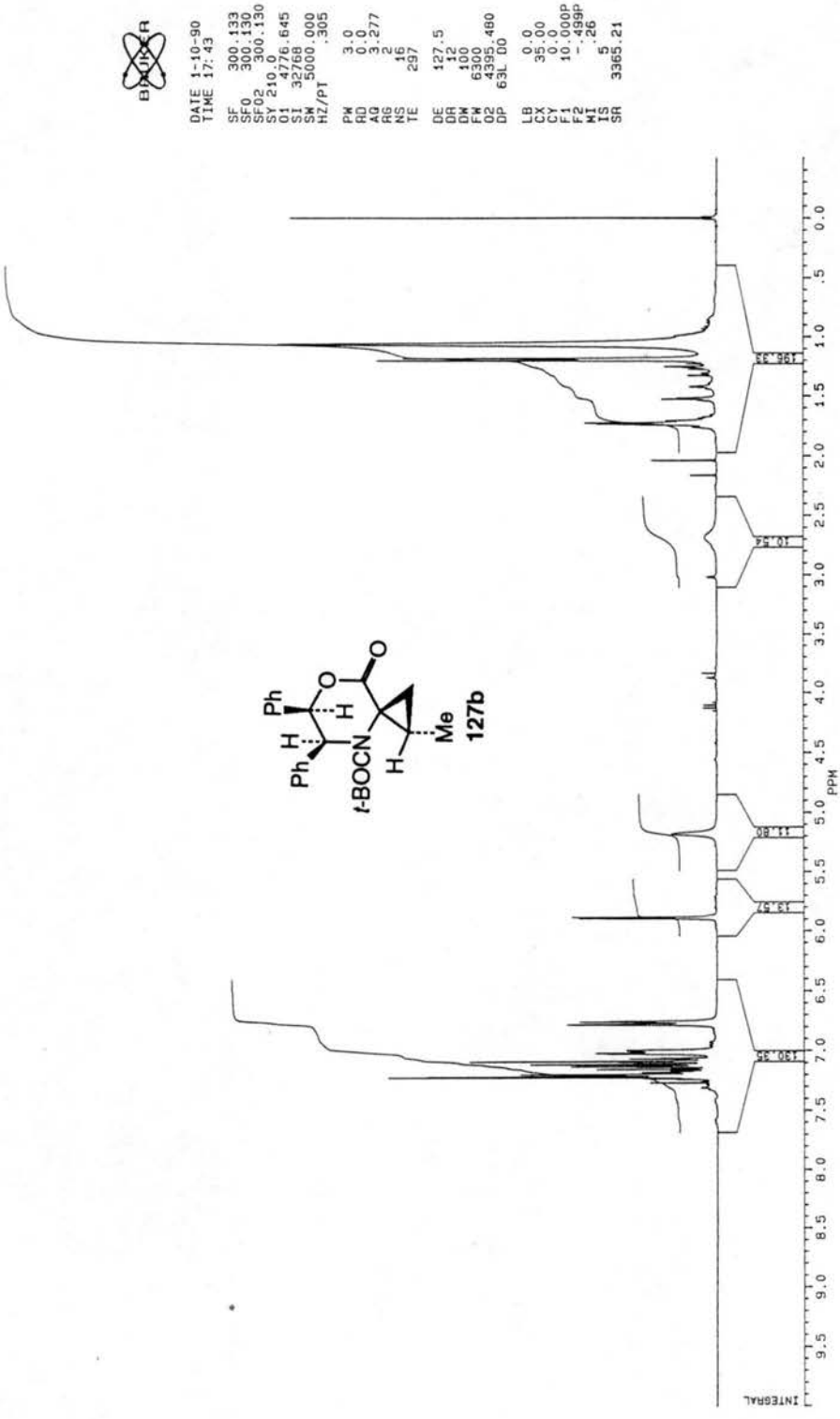

Ph
H
Ph
O
O
H
t-BOCN
H
NO2
126g
PPM

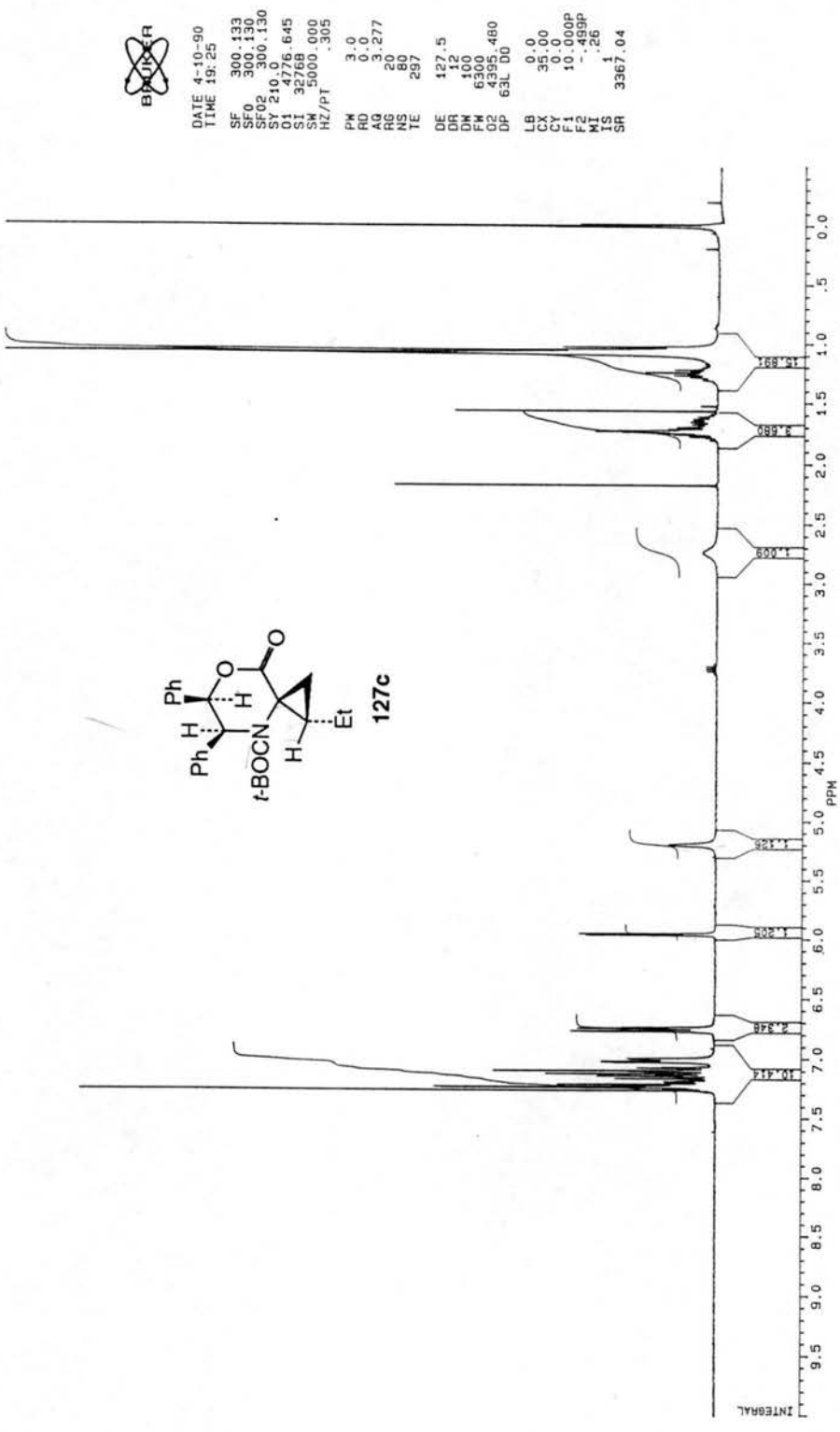

DATE 15-3-92
SF 300.133
SW 210.0
SI 4776.645
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0
AG 3.277
RG 80
NS 56
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
HZ/CM -.498P
PPM/CM 90.036
SR 3367.95
Ph
H
O
O
Ph
H
t-BOCN
OMe
126h
PPM
INTEGRAL

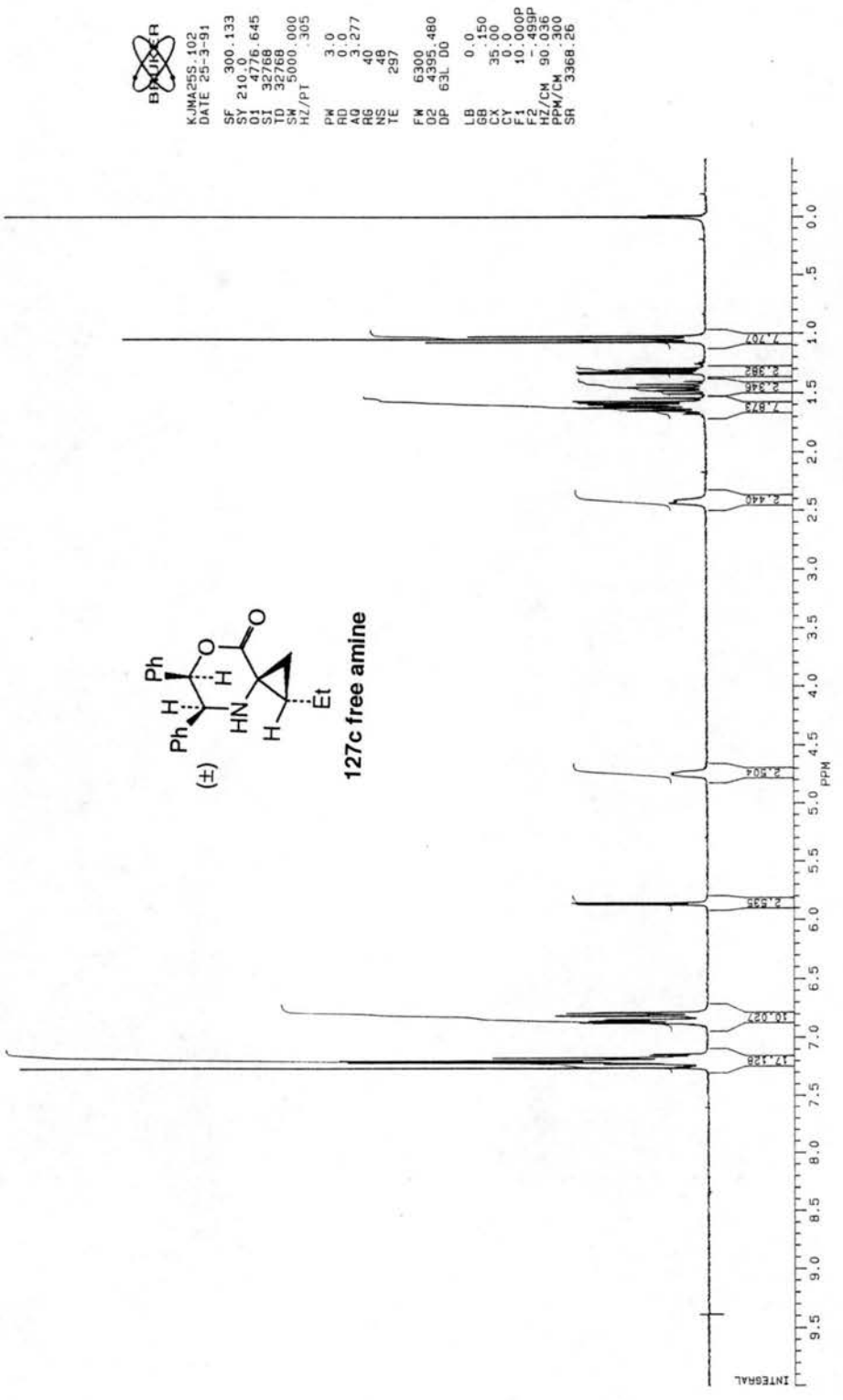

OCT29JSC.001
DATE 11 3 92
SF 300.133
SX 210.0
O1 1476.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
NS 20
RG 16
TE 297
FW 6300
D2 4395.480
DP 63L PD
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3366.73
Ph
H
Ph
O
H
O
N
t-BOC
OMe
OMe
126l
PPM

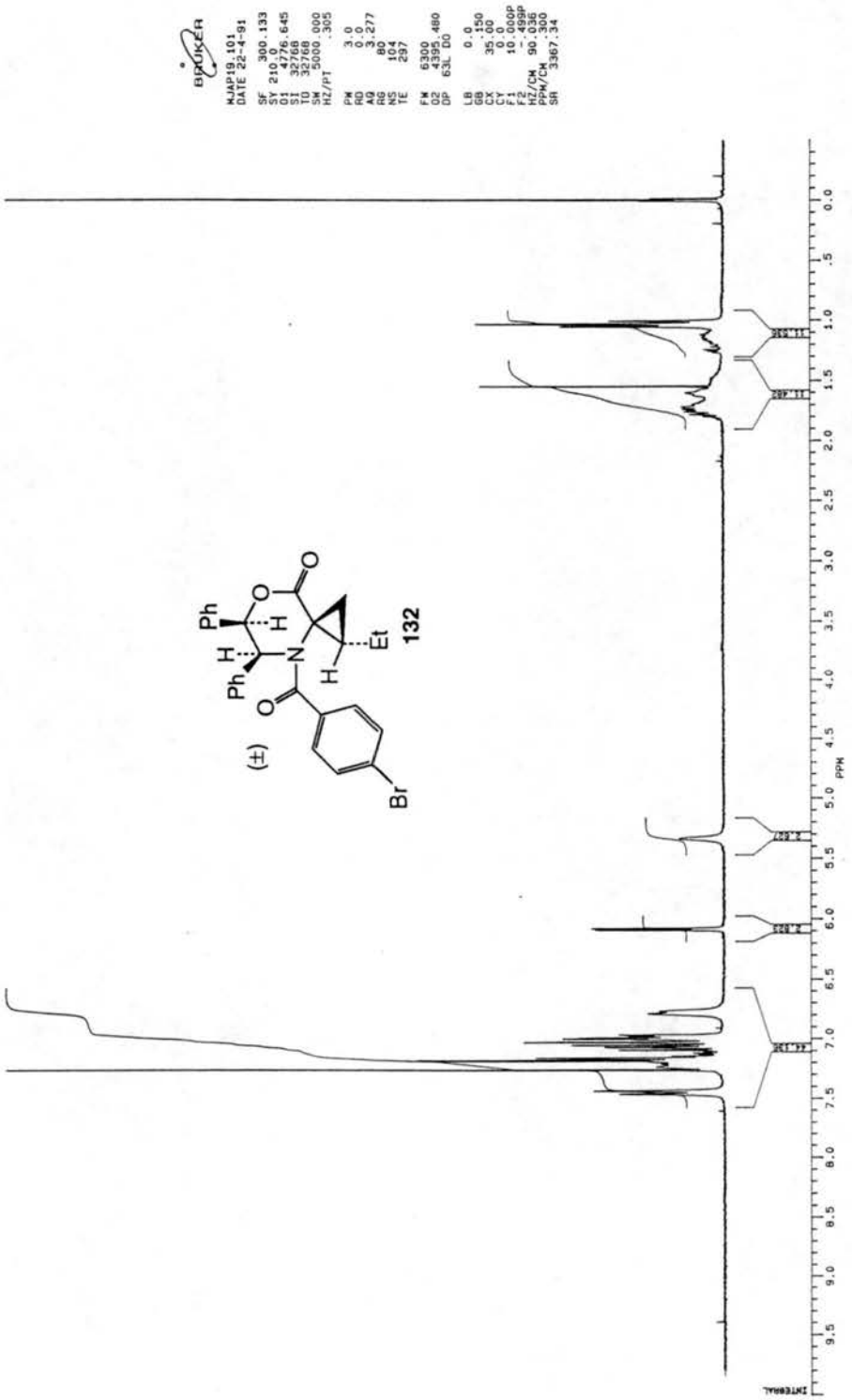

Ph
H
Ph
O
t-BOCN
H
O
D
D
+
Ph
H
Ph
O
t-BOCN
H
O
D
D
(3S)/(3R)-127a
Ratio: 11:1
BRUKER
KAN1
DATE 3-10-90
TIME 17:46
SF 300.135
SF0 300.130
SF02 300.130
SY 210.0
O1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 10
NS 32
TE 297
DE 127.5
DR 12
DW 100
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
MI .26
IS 0
SR 4787.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

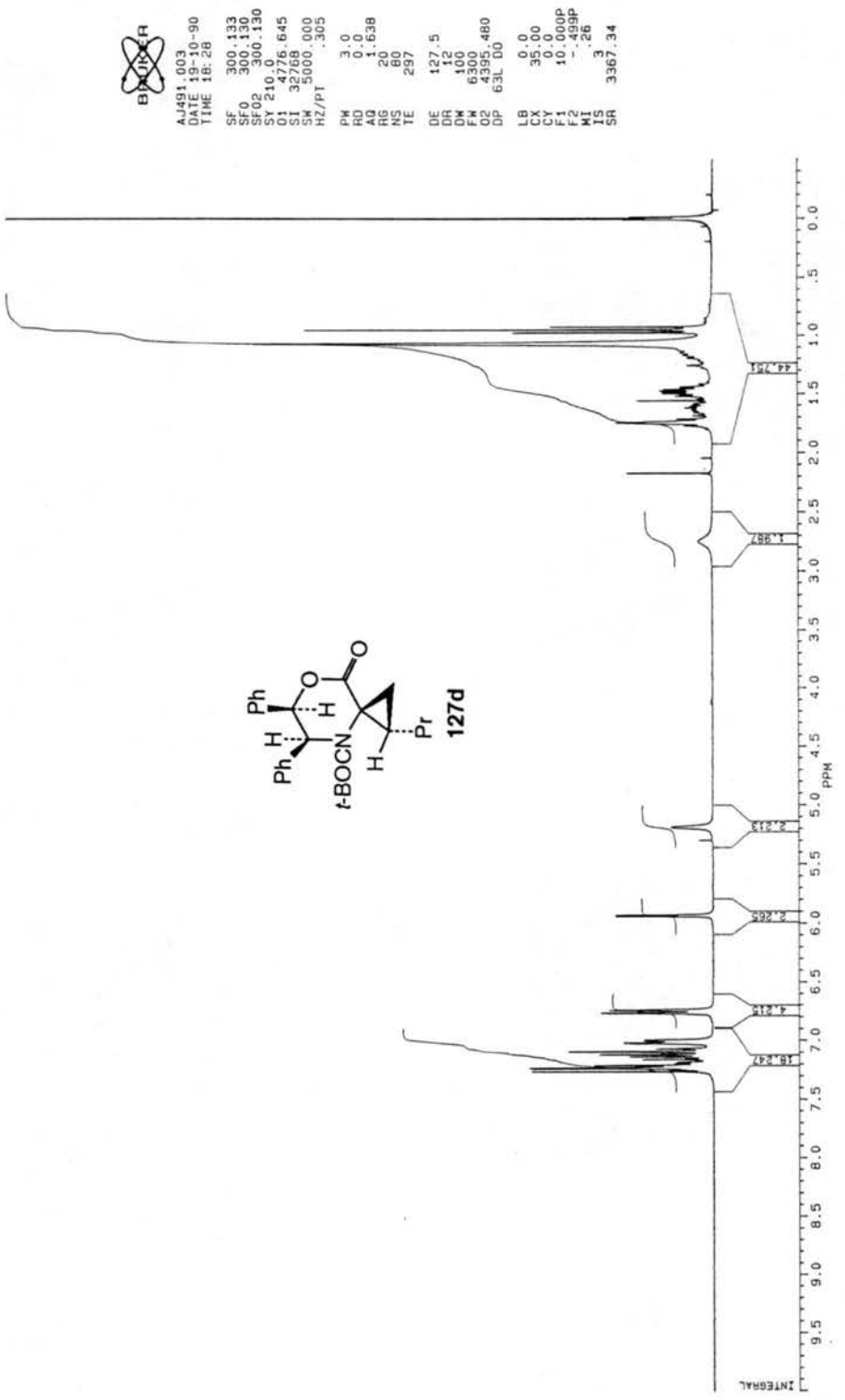

DATE 10-7-90
TIME 17:11
SF 300.133
SFO 300.130
SF02 300.130
SY 210.0
O1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 5.0
RD 0.0
AQ 3.277
RG 4
NS 32
TE 297
DE 127.5
DA 12
DW 100
FW 6300
O2 4800.000
DP 63L PO
LB 0.0
CX 35.00
CY 0.0
F1 -40.000P
F2 -.499P
MI .26
IS 4
SR 3369.48
Ph
H
O
H
HN
D
D
+
130/131
PPM
INTEGRAL

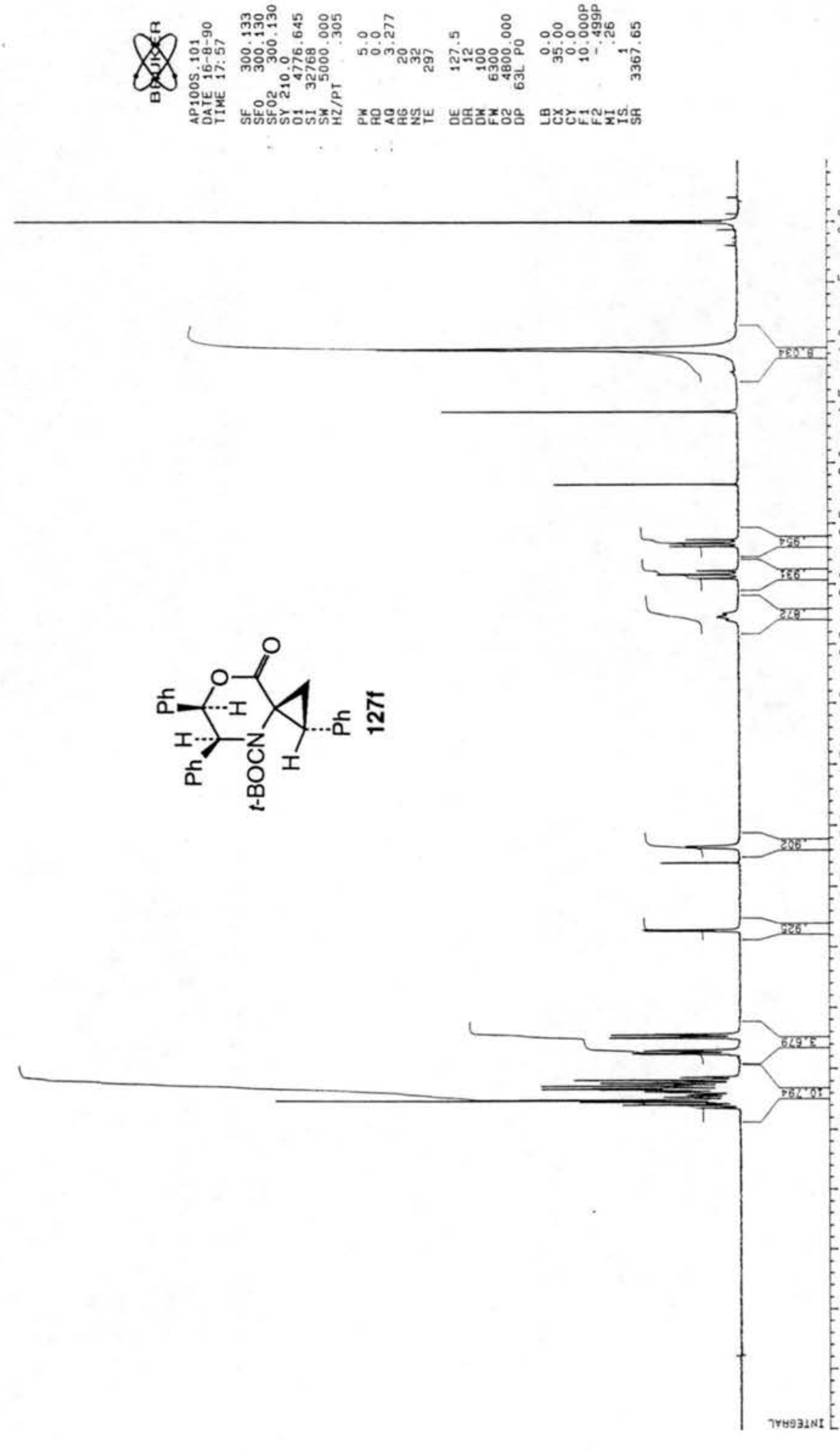

DATE 1-10-90
TIME 17:43
SF 300.133
SFO 300.130
SFO2 300.130
SY 210.0
O1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 2
NS 16
TE 297
DE 127.5
DA 12
DW 100
FW 6300
O2 4395.480
DP 63L 00
LB 0.0
CX 35.00
CY 0.00
F1 10.000P
F2 -.499P
MI .26
IS 5
SR 3365.21
Ph
H
O
H
Ph
t-BOCN
H
Me
127b
INTEGRAL
PPM

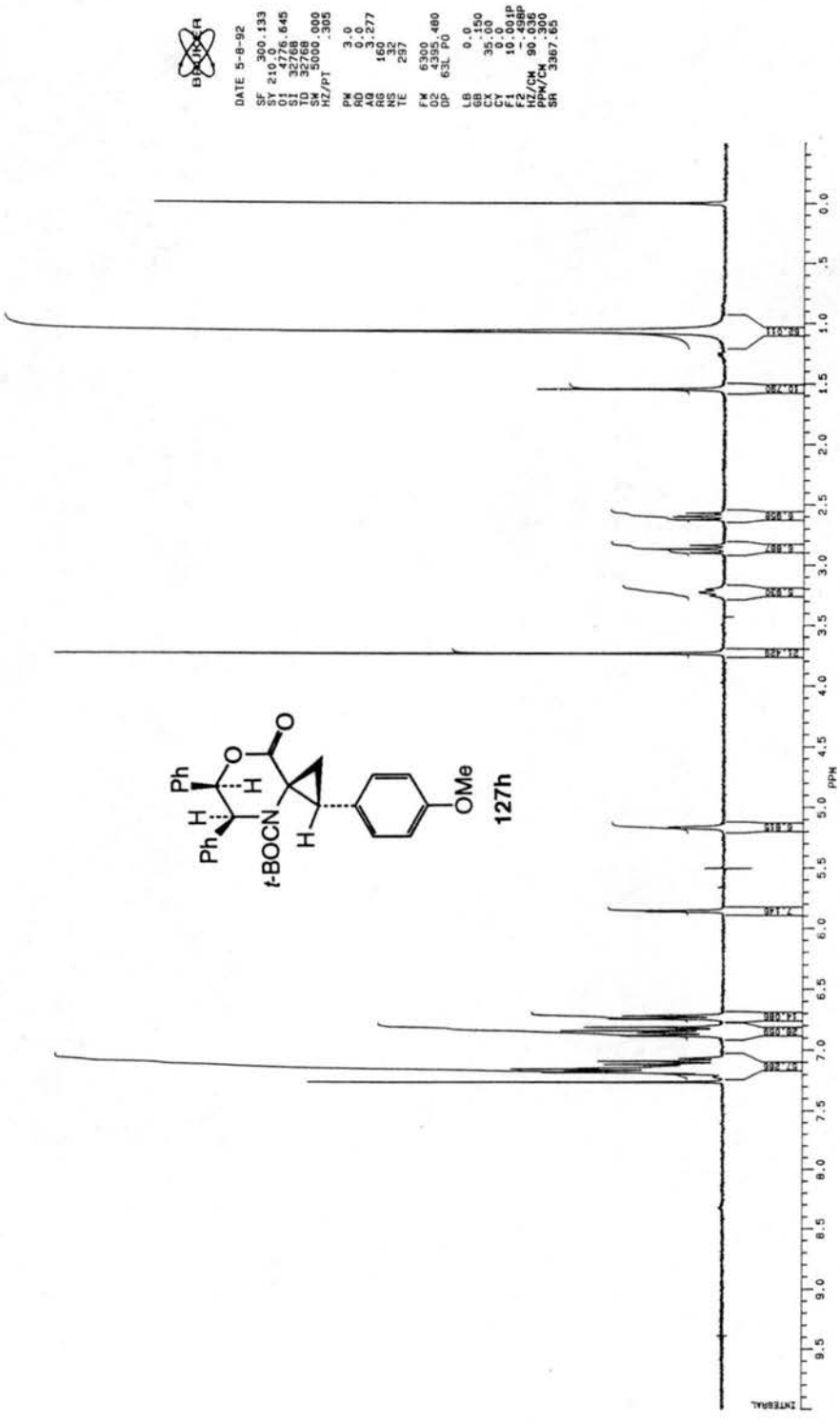

BRUKER
DATE 4-10-90
TIME 19.25
SF 300.133
SFO 300.130
SFO2 300.130
SY 210.0
O1 4776.645
SI 32768.000
SW 5000.305
HZ/PT
PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 80
TE 297
DE 127.5
DR 12
DW 100
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
MI .26
IS 1
SR 3367.04
Ph
H
O
O
Ph
H
t-BOCN
H
Et
127c
15.891
3.680
6.009
1.126
1.205
2.348
10.414
INTEGRAL
PPM

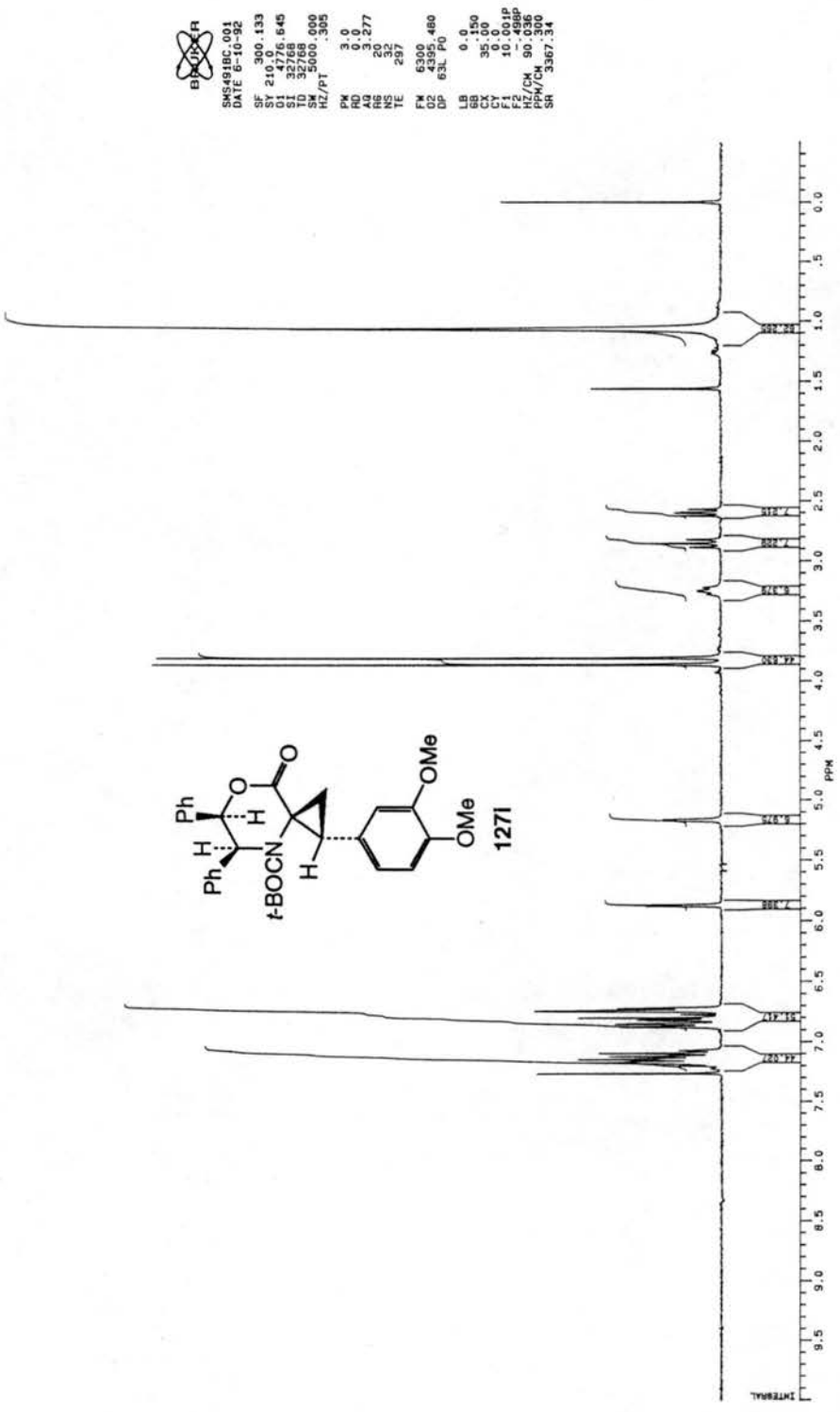

BRUKER
KJMA255.102
DATE 25-3-91
SF 300.133
SY 210.0
01 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 40
NS 48
TE 297
FW 6300
O2 4395.480
DP 63L 00
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 3368.26
Ph
H
O
H
Ph
HN
H
Et
(±)
127c free amine
7.707
7.382
7.346
7.878
2.440
2.404
2.436
10.027
17.128
INTEGRAL
PPM

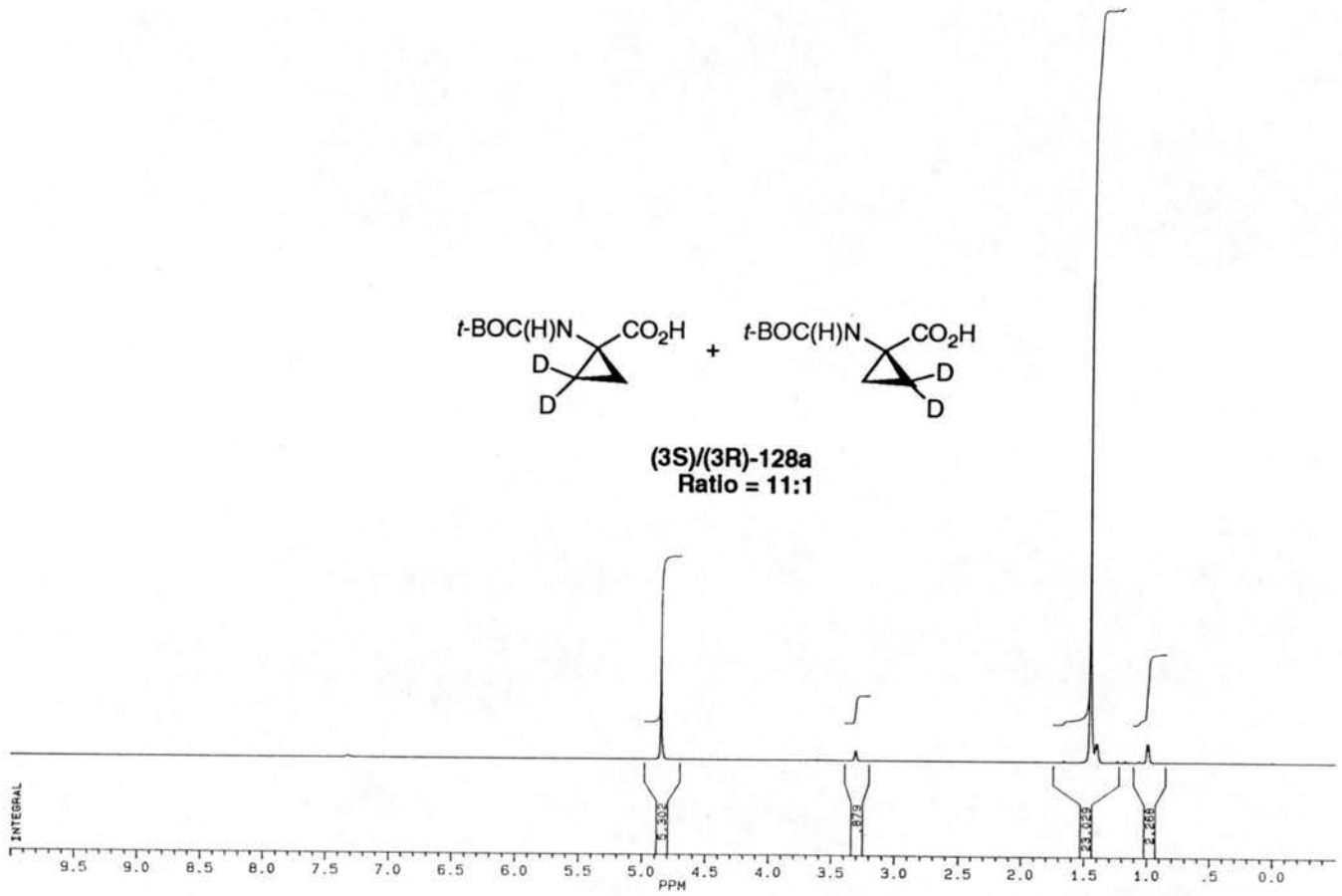

BRUKER
MJAP19.101
DATE 22-4-91
SF 300.133
SY 210.0
01 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 80
NS 104
TE 297
FW 6300
D2 4995.480
DP 63L 00
LB .0
GB .150
CX 35.00
CY 0
F1 10.000P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
Ph
H
O
O
H
Ph
N
O
H
Et
(±)
Br
132
PPM
INTEGRAL


BRUKER
AJ491.003
DATE 19-10-90
TIME 18:28
SF 300.133
SFO 300.130
SFO2 300.130
SY 210.0
O1 4776.645
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 1.638
RG 20
NS 80
TE 297
DE 127.5
DA 12
DW 100
FW 6300
O2 4395.480
DP 63L DO
LB 0.0
CX 35.00
CY 0.00
F1 10.000P
F2 -.49P
MI -.26
IS 3
SR 3367.34
Ph
H
Ph
O
H
t-BOCN
H
Pr
127d
INTEGRAL
PPM


127f


BRUKER
DATE 5-8-92
SF 300.133
SY 210.0
OF 1776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 160
NS 32
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3367.65
Ph
H
O
O
H
Ph
t-BOCN
H
OMe
127h
PPM
INTEGRAL


Ph
H
O
O
Ph
H
t-BOCN
H
OMe
OMe
127l
ppm



BRUKER

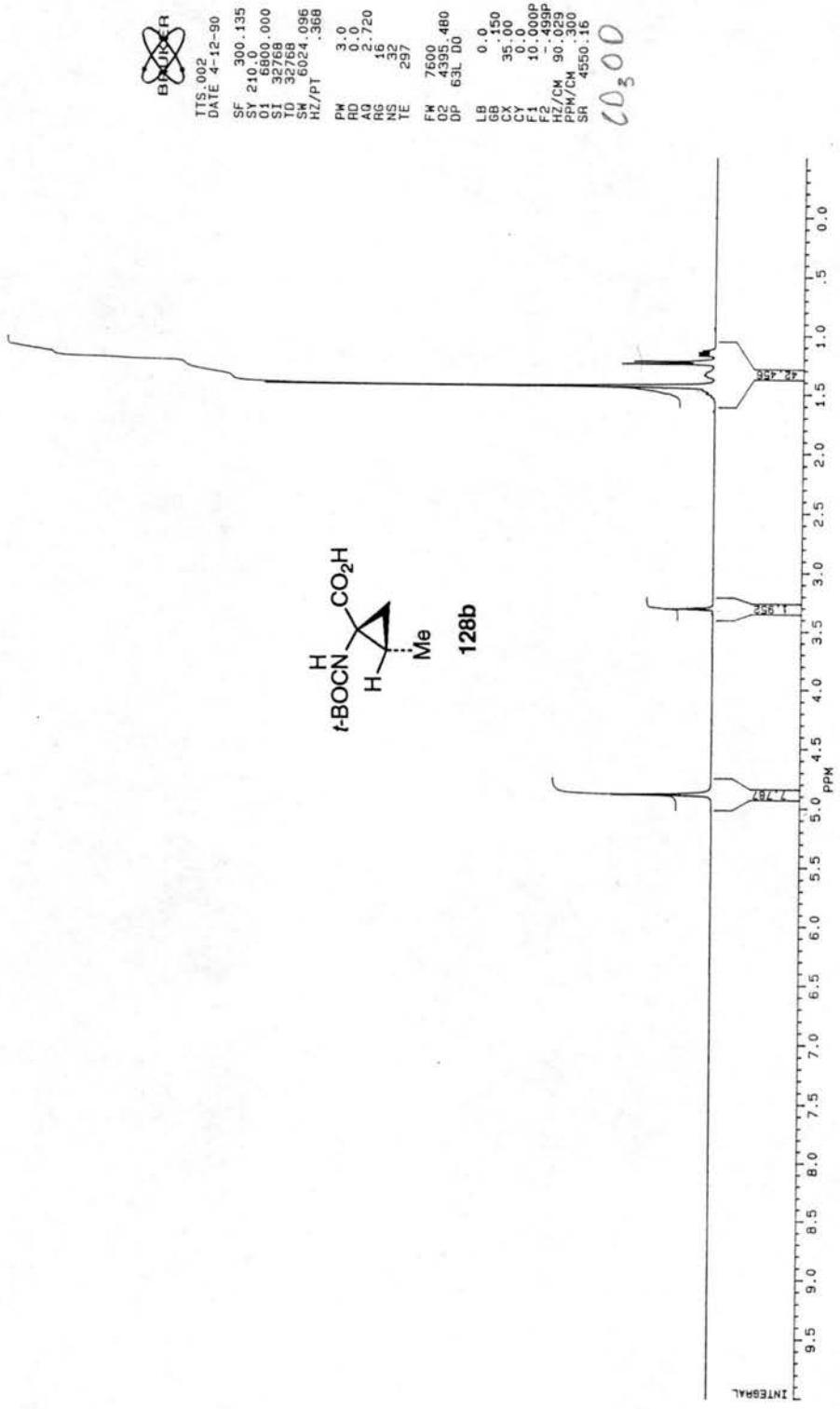
TTS.001
DATE 8-12-90

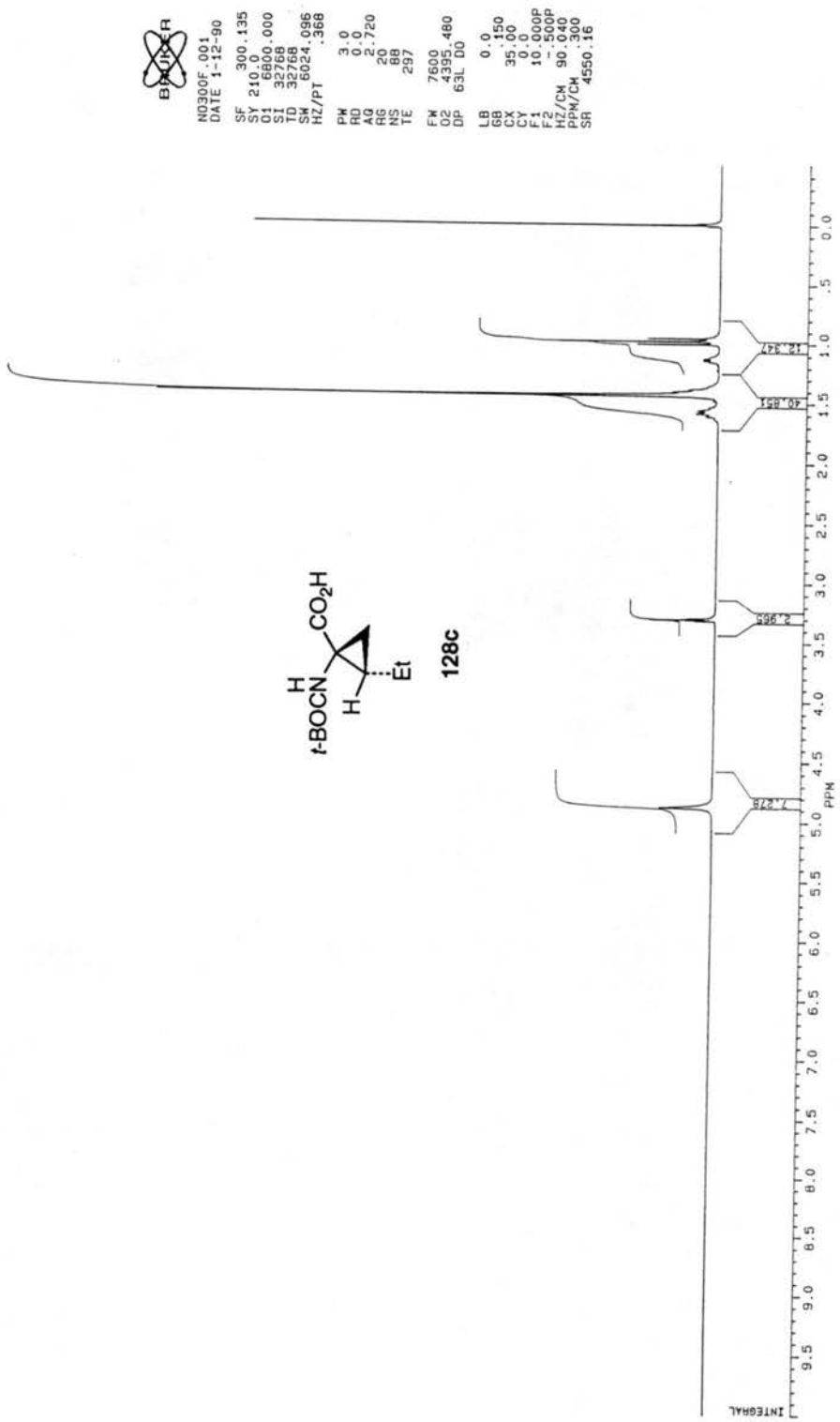
SF 300.135
SY 210.0
O1 6800.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368

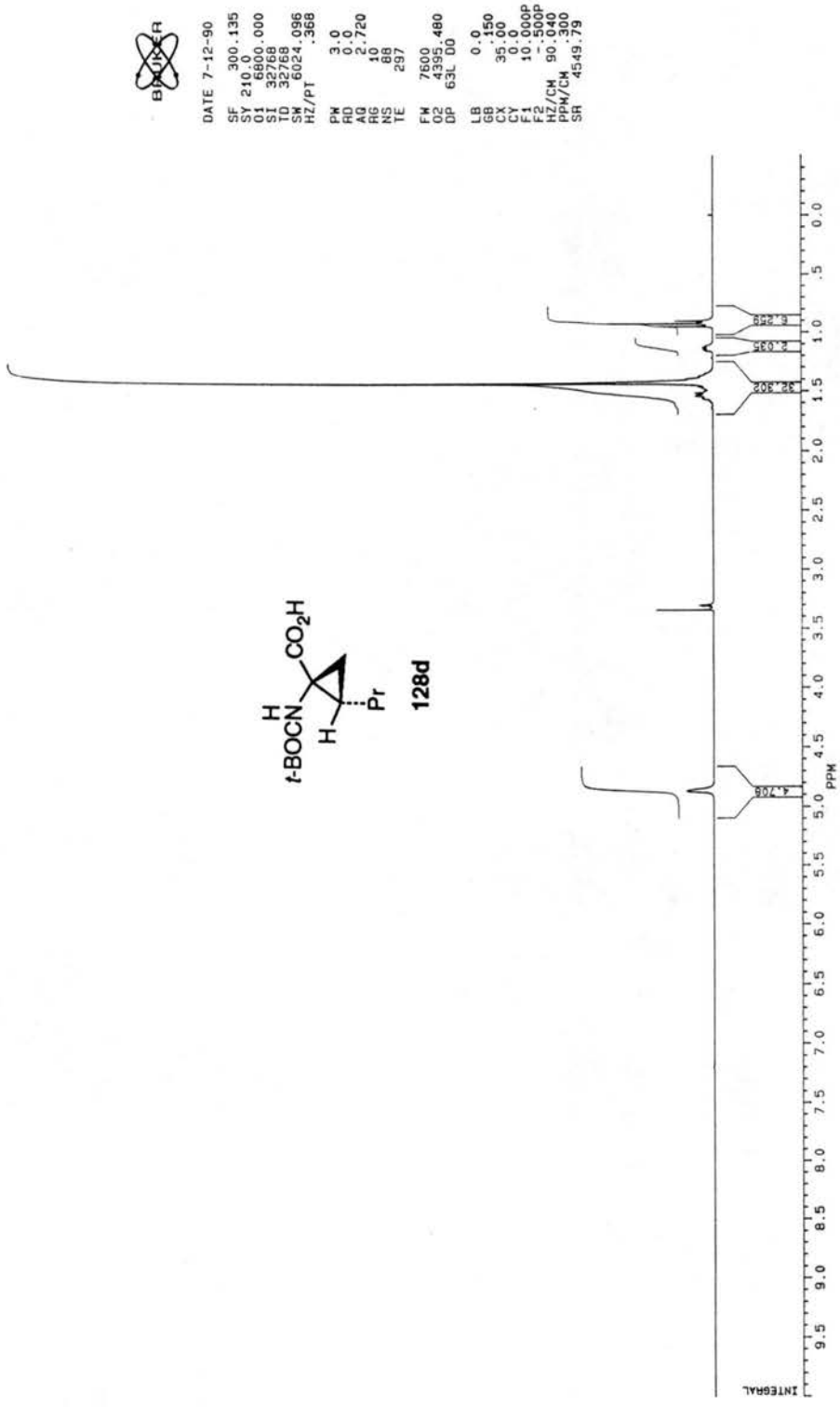
PW 3.0
RD 0.0
AQ 2.720
RG 20
NS 24
TE 297

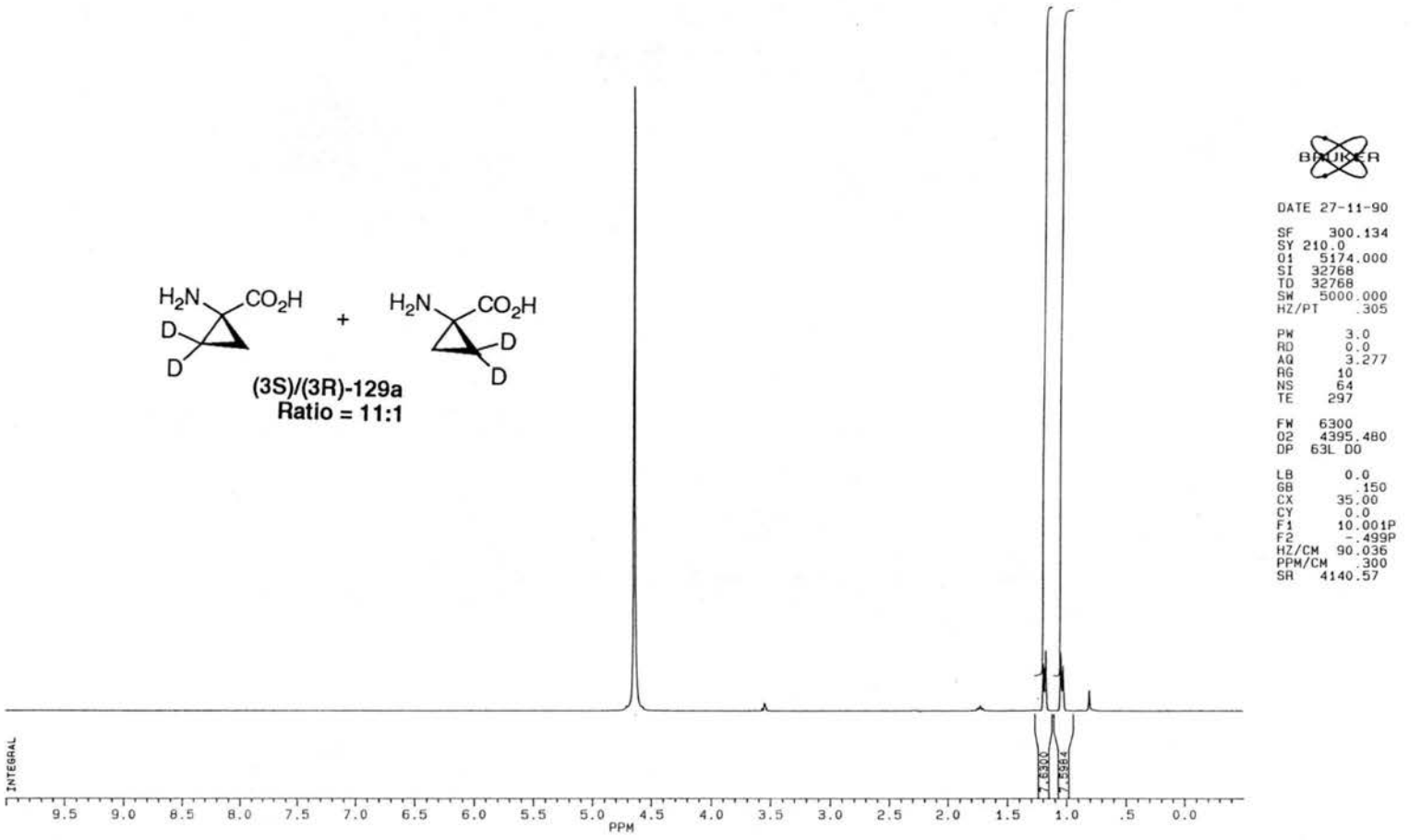
FW 7600
O2 4395.480
DP 63L DO

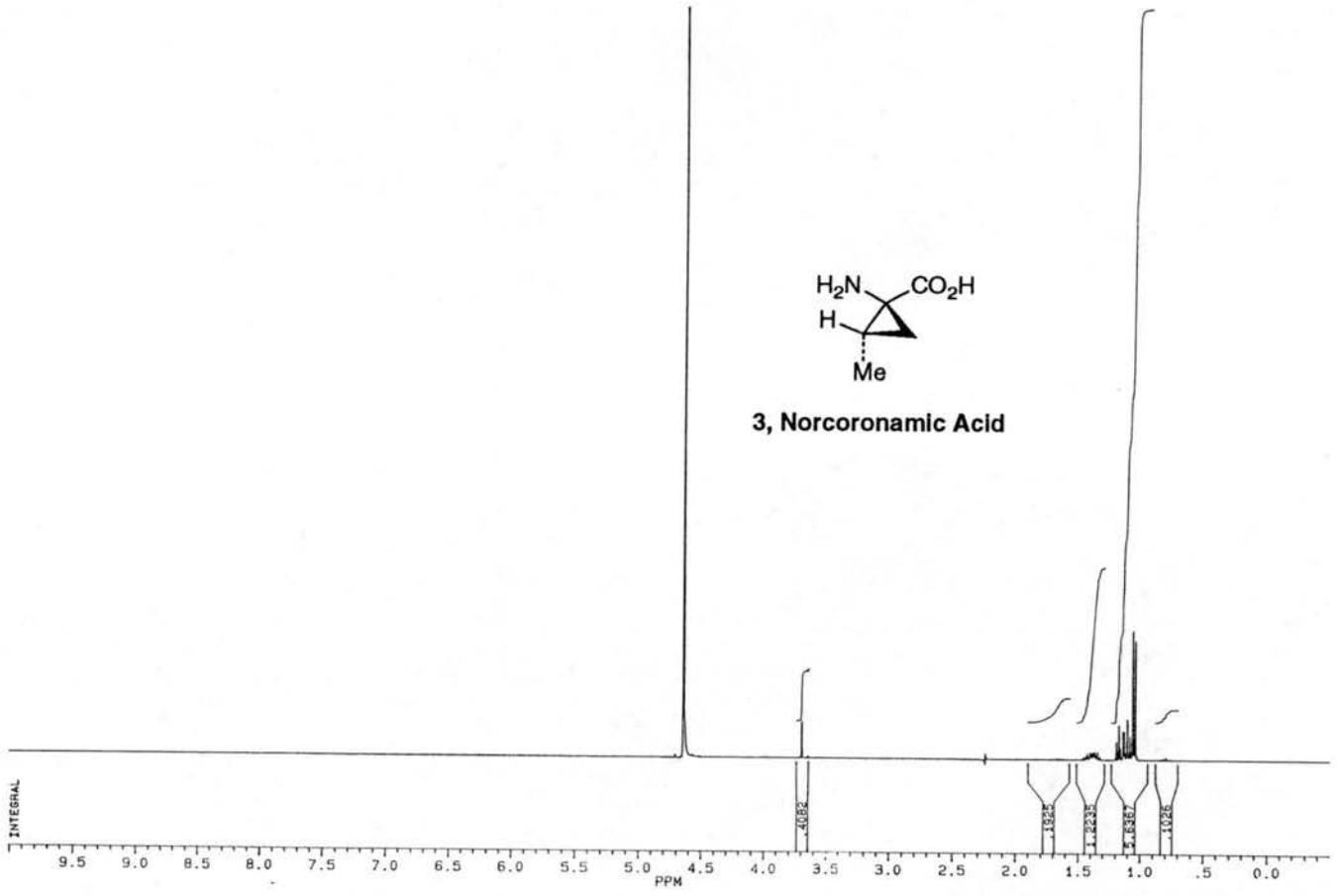
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.500P
HZ/CM 90.040
PPM/CM .300
SR 4550.16


BRUKER
TTS.002
DATE 4-12-90
SF 300.135
SY 210.0
O1 6800.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AQ 2.720
RG 16
NS 32
TE 297
FW 7600
O2 4395.480
DP 63L DO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.459P
HZ/CM 90.929
PPM/CM 7.300
SR 4550.16
CD3OD
42.456
1.952
7.787
INTEGRAL
PPM
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
H
t-BOCN
CO2H
H
Me
128b


BRUKER
N0300F.001
DATE 1-12-90
SF 300.135
SY 210.0
01 6800.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AQ 2.720
RG 20
NS 88
TE 297
FW 7600
02 4395.480
DP 63L DO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.000P
F2 -.500P
HZ/CM 90.040
PPM/CM .300
SR 4550.16
12.347
40.851
2.984
7.978
INTEGRAL
PPM
t-BOCN
CO2H
H
H
Et
128c

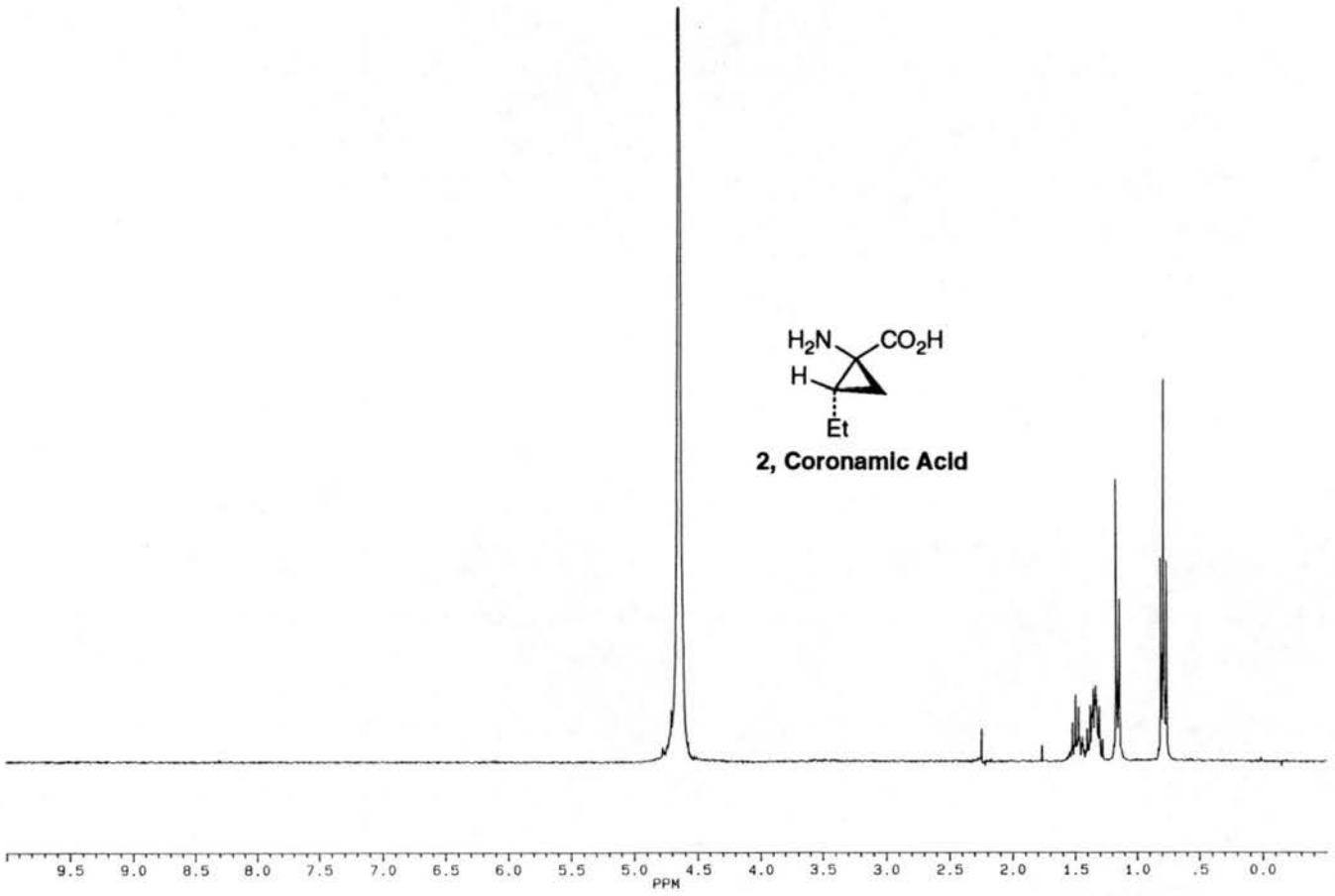

BRUKER
DATE 7-12-90
SF 300.135
SY 210.0
O1 6800.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AQ 2.720
RG 10
NS 88
TE 297
FW 7600
O2 4395.480
DP 63L 00
LB 0.0
GB .150
CX 35.00
CY 0.000P
F1 10.500P
F2 90.040
HZ/CM .300
PPM/CM 4549.79
SR
32.302
2.035
2.249
4.708
INTEGRAL
PPM
t-BOCN
H
CO2H
H
Pr
128d


H2N
CO2H
D
D
+
H2N
CO2H
D
D
(3S)/(3R)-129a
Ratio = 11:1
INTEGRAL
7.6300
7.6964
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM
DATE 27-11-90
SF 300.134
SY 210.0
O1 5174.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 10
NS 64
TE 297
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 4140.57



DATE 23-11-90

SF	300.134
SY	210.0
O1	5174.000
SI	32768
TD	32768
SW	5000.000
HZ/PT	.305
PW	3.0
RD	0.0
AQ	3.277
RG	16
NS	32
TE	297
FW	6300
O2	4395.480
DP	63L D0
LB	0.0
GB	.150
CX	35.00
CY	0.0
F1	10.002P
F2	-.498P
HZ/CM	90.036
PPM/CM	.300
SR	4141.49



BRUKER

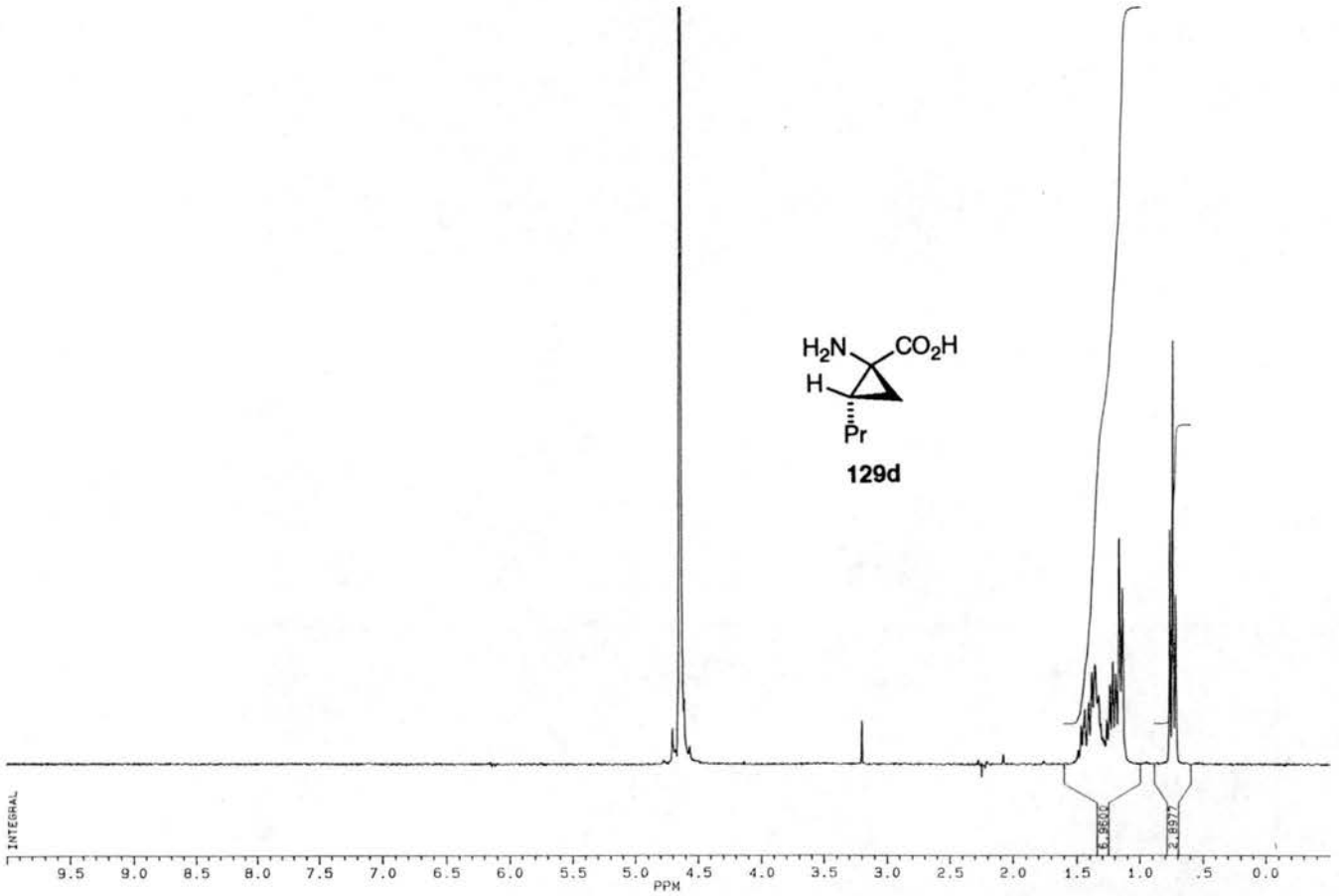
DATE 12-12-90

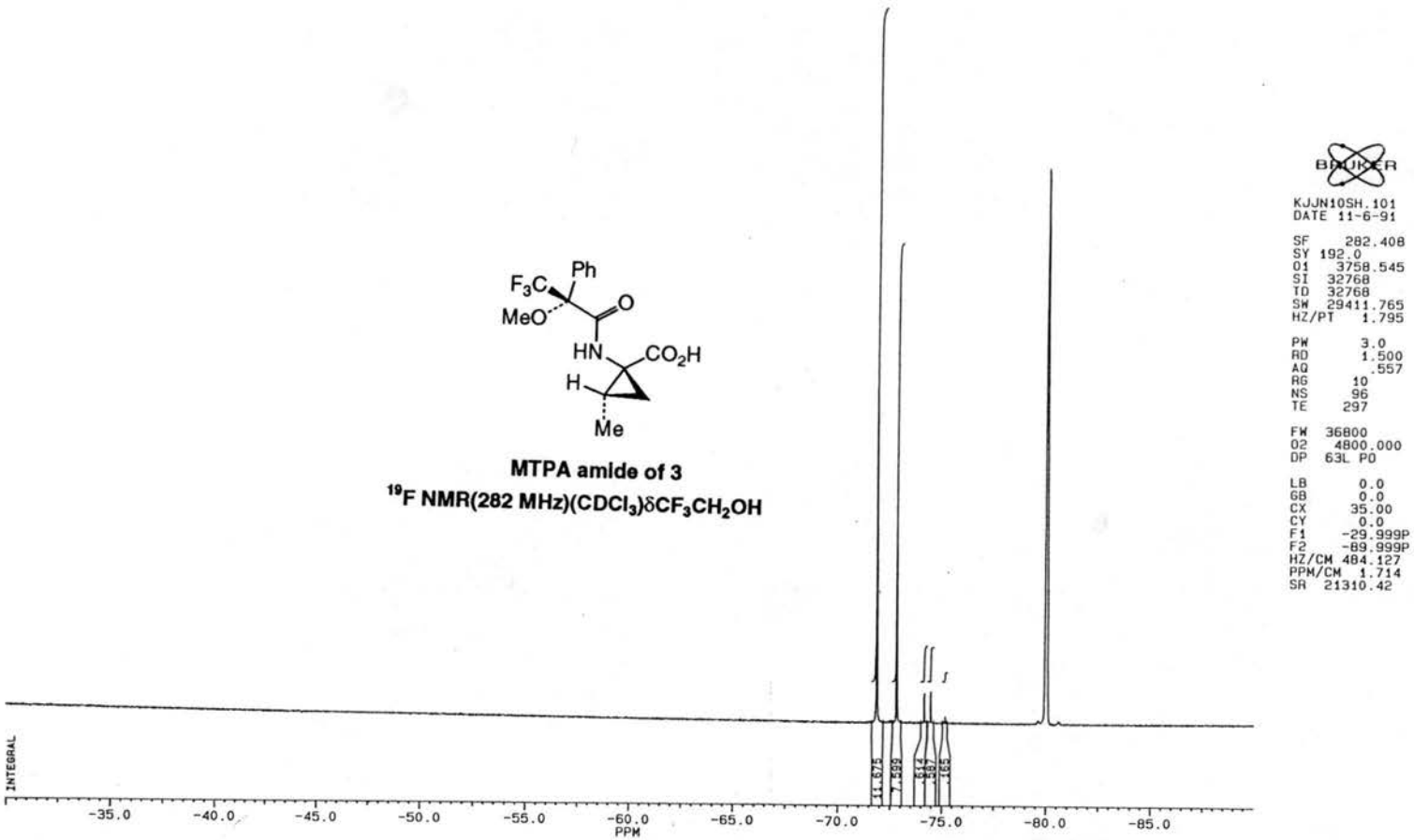
SF 300.134
SY 210.0
O1 5174.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368

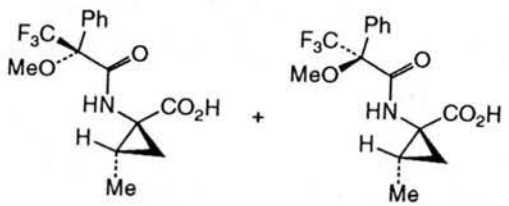
PW 3.0
RD 0.0
AQ 2.720
RG 20
NS 400
TE 297

FW 7600
O2 4395.480
DP 63L DO

LB 0.0
GB .300
CX 35.00
CY 0.0
F1 10.001P
F2 -.499P
HZ/CM 90.040
PPM/CM .300
SR 4140.60


H2N
CO2H
H
Pr
129d
INTEGRAL
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM
BRUKER
LB.403
DATE 5-12-90
SF 300.134
SY 210.0
O1 5174.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 104
TE 297
FW 6300
O2 4395.480
DP 63L D0
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.499P
HZ/CM 90.036
PPM/CM .300
SR 4140.87


Ph
F3C
MeO
O
HN
CO2H
H
Me
MTPA amide of 3
19F NMR(282 MHz)(CDCl3)δCF3CH2OH
BRUKER
KJJN10SH.101
DATE 11-6-91
SF 282.408
SY 192.0
01 3758.545
SI 32768
TD 32768
SW 29411.765
HZ/PT 1.795
PW 3.0
RD 1.500
AQ .557
RG 10
NS 96
TE 297
FW 36800
02 4800.000
DP 63L PO
LB 0.0
GB 0.0
CX 35.00
CY 0.0
F1 -29.999P
F2 -89.999P
HZ/CM 484.127
PPM/CM 1.714
SR 21310.42
INTEGRAL
11.675
7.599
6.14
5.587
1.65
-35.0
-40.0
-45.0
-50.0
-55.0
-60.0
-65.0
-70.0
-75.0
-80.0
-85.0
PPM



MTPA amide of 3

^{19}F NMR(282 MHz)($CDCl_3$)δCF_3CH_2OH

BRUKER

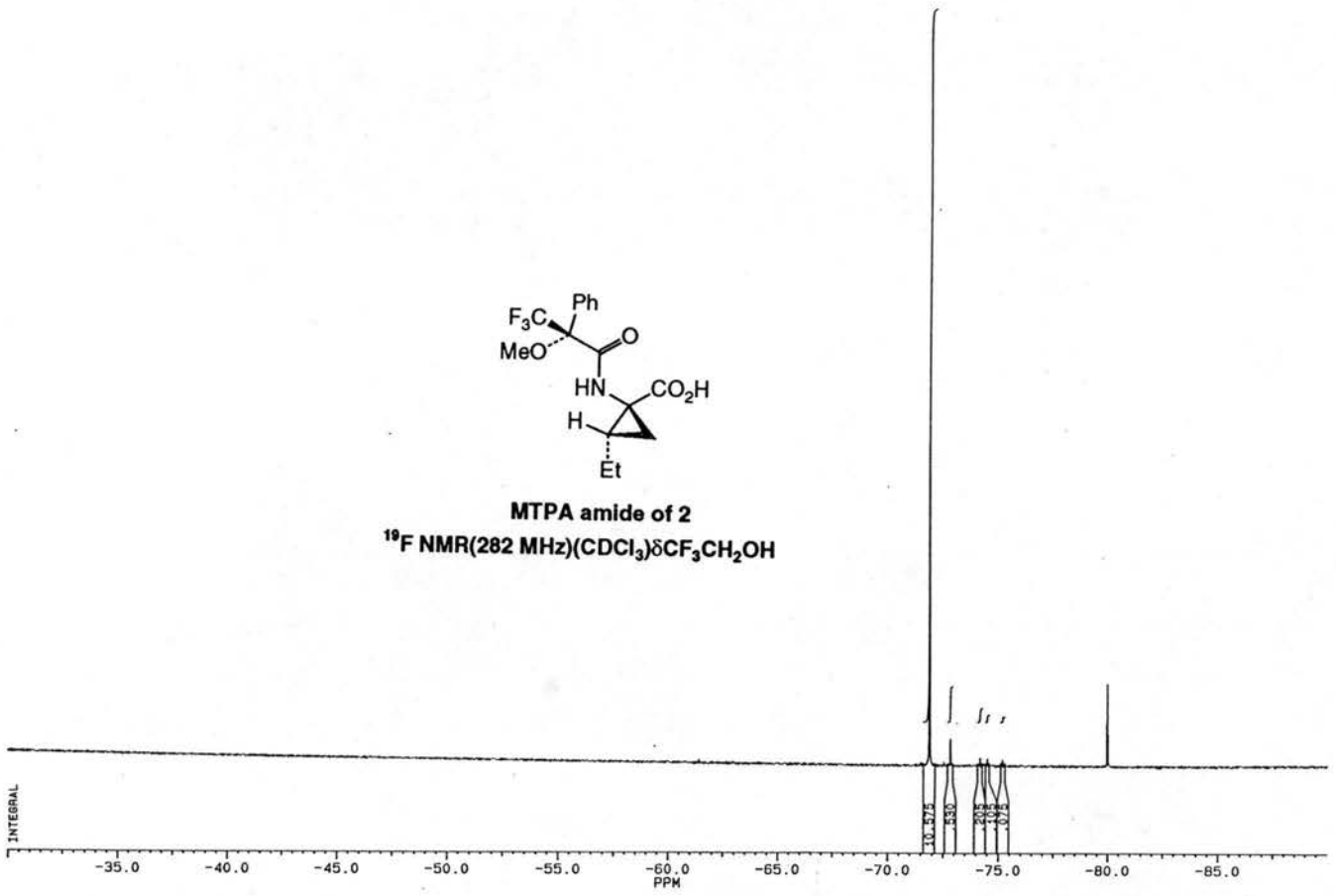
SDSE75.001
DATE 7-9-92

SF 282.408
SY 192.0
01 11280.000
SI 32768
TD 32768
SW 29411.765
HZ/PT 1.795

PW 3.0
RD 1.500
AQ .557
RG 10
NS 64
TE 297

FW 36800
02 4800.000
DP 63L PO

LB 0.0
GB 0.0
CX 35.00
CY 0.0
F1 -29.999P
F2 -89.999P
HZ/CM 484.127
PPM/CM 1.714
SR 21356.87



BRUKER

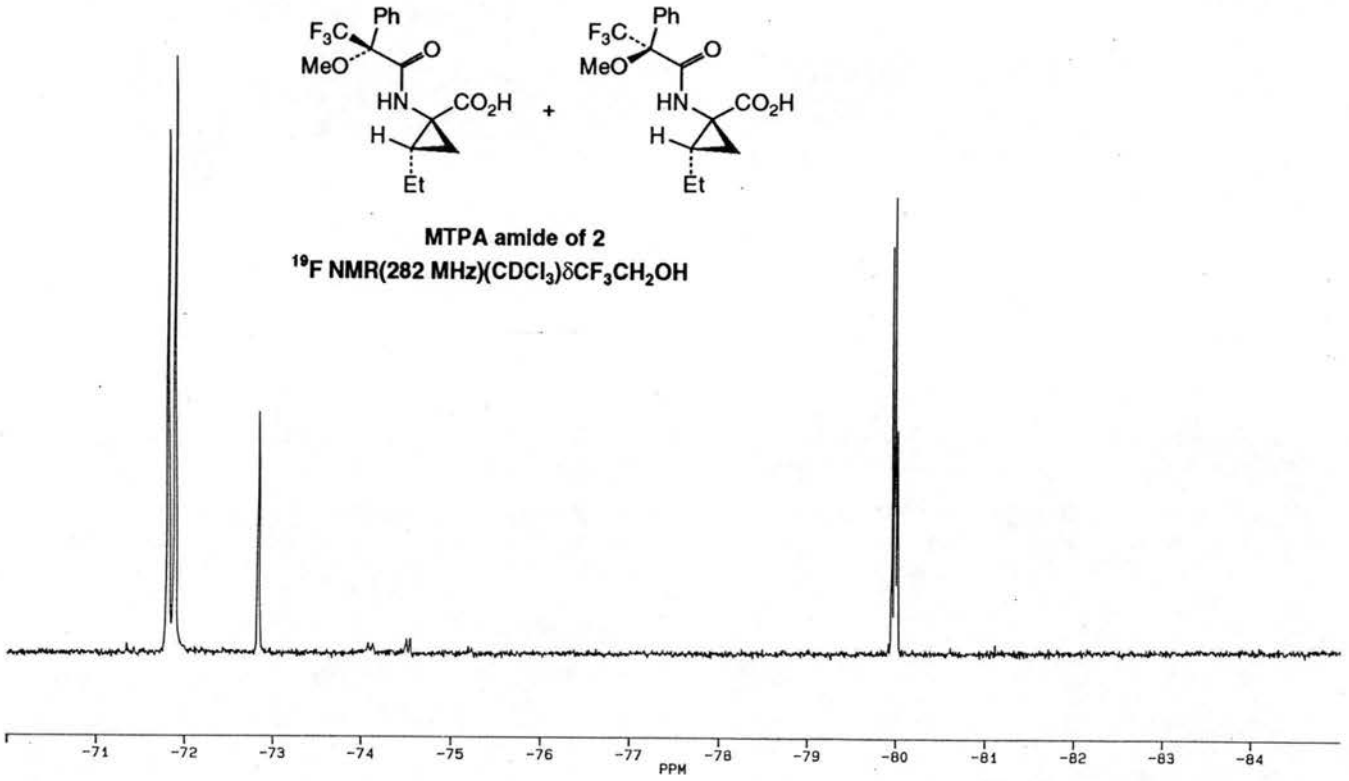
KJJN10SH.101
DATE 11-6-91

SF 282.408
SY 192.0
O1 3758.545
SI 32768
TD 32768
SW 29411.765
HZ/PT 1.795

PW 3.0
RD 1.500
AQ .557
RG 8
NS 56
TE 297

FW 36800
O2 4800.000
DP 63L P0

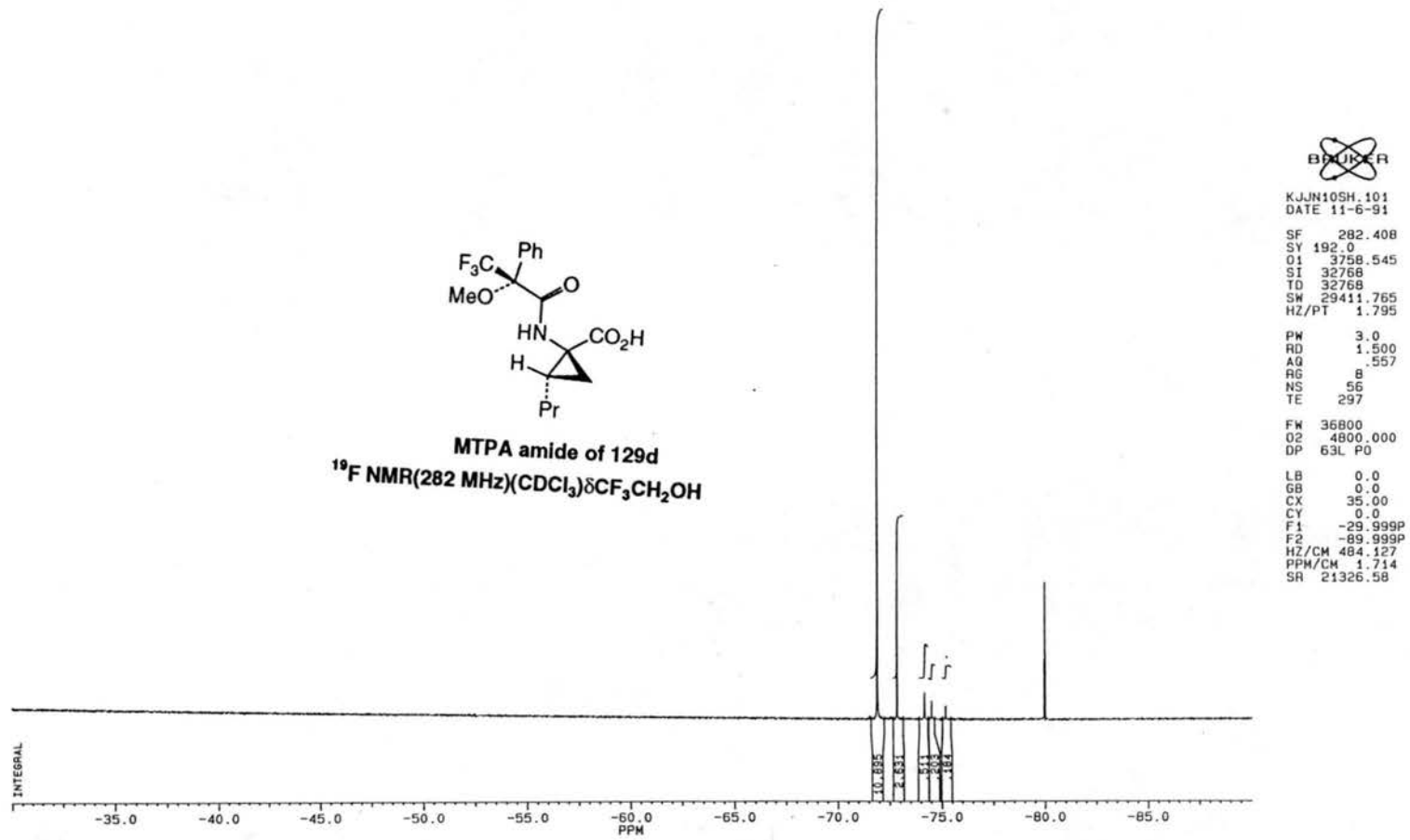
LB 0.0
GB 0.0
CX 35.00
CY 0.0
F1 -29.999P
F2 -89.999P
HZ/CM 484.127
PPM/CM 1.714
SR 21326.58

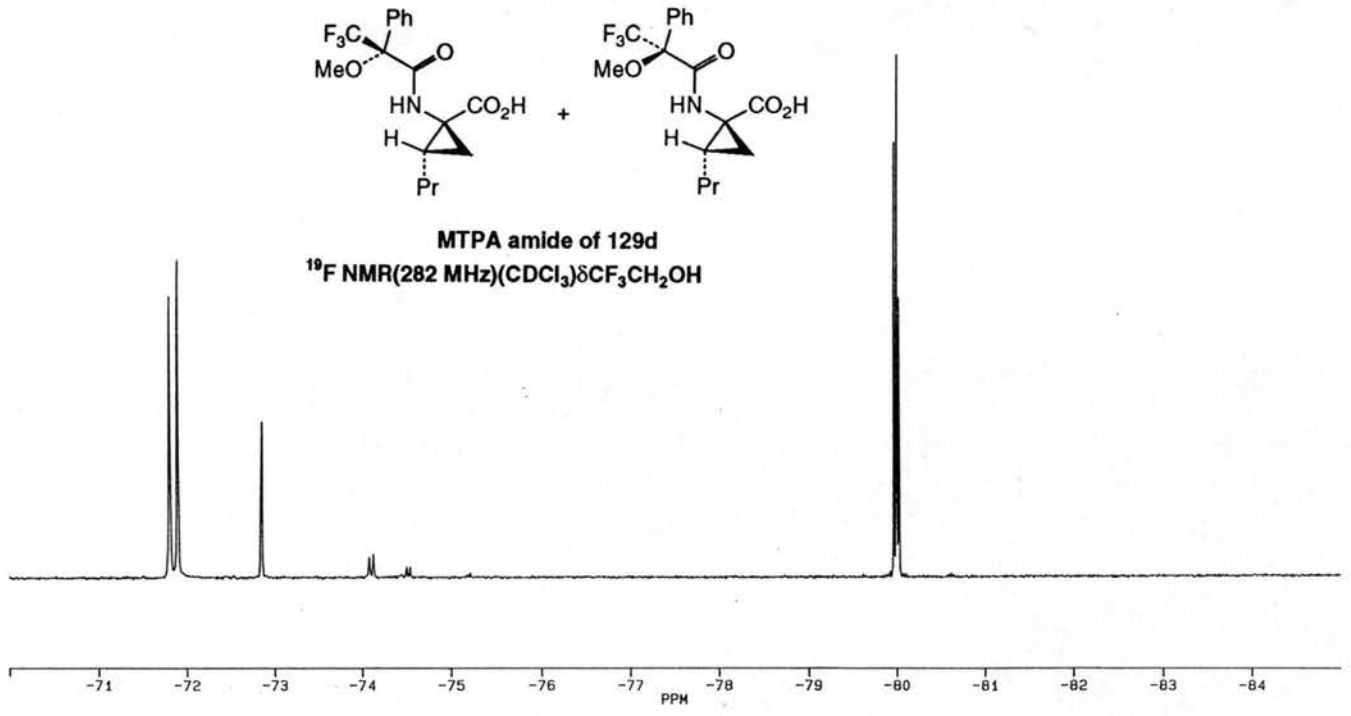


BRUKER

SEPF539.005
DATE 12-9-92

SF	282.408
SY	192.0
O1	11280.000
SI	32768
TD	32768
SW	29411.765
HZ/PT	1.795
PW	3.0
RD	1.500
AQ	.557
RG	20
NS	32
TE	297
FW	36800
O2	4800.000
DP	63L PO
LB	0.0
GB	0.0
CX	35.00
CY	0.0
F1	-70.001P
F2	-84.996P
HZ/CM	120.993
PPM/CM	.428
SR	21322.76


F3C
Ph
MeO
O
HN
CO2H
H
Pr
MTPA amide of 129d
19F NMR(282 MHz)(CDCl3)δCF3CH2OH
KJJN10SH.101
DATE 11-6-91
SF 282.408
SY 192.0
O1 3758.545
SI 32768
TD 32768
SW 29411.765
HZ/PT 1.795
PW 3.0
RD 1.500
AQ .557
RG 8
NS 56
TE 297
FW 36800
O2 4800.000
DP 63L PO
LB 0.0
GB 0.0
CX 35.00
CY 0.0
F1 -29.999P
F2 -89.999P
HZ/CM 484.127
PPM/CM 1.714
SR 21326.58
INTEGRAL
-35.0
-40.0
-45.0
-50.0
-55.0
-60.0
-65.0
-70.0
-75.0
-80.0
-85.0
PPM



BRUKER

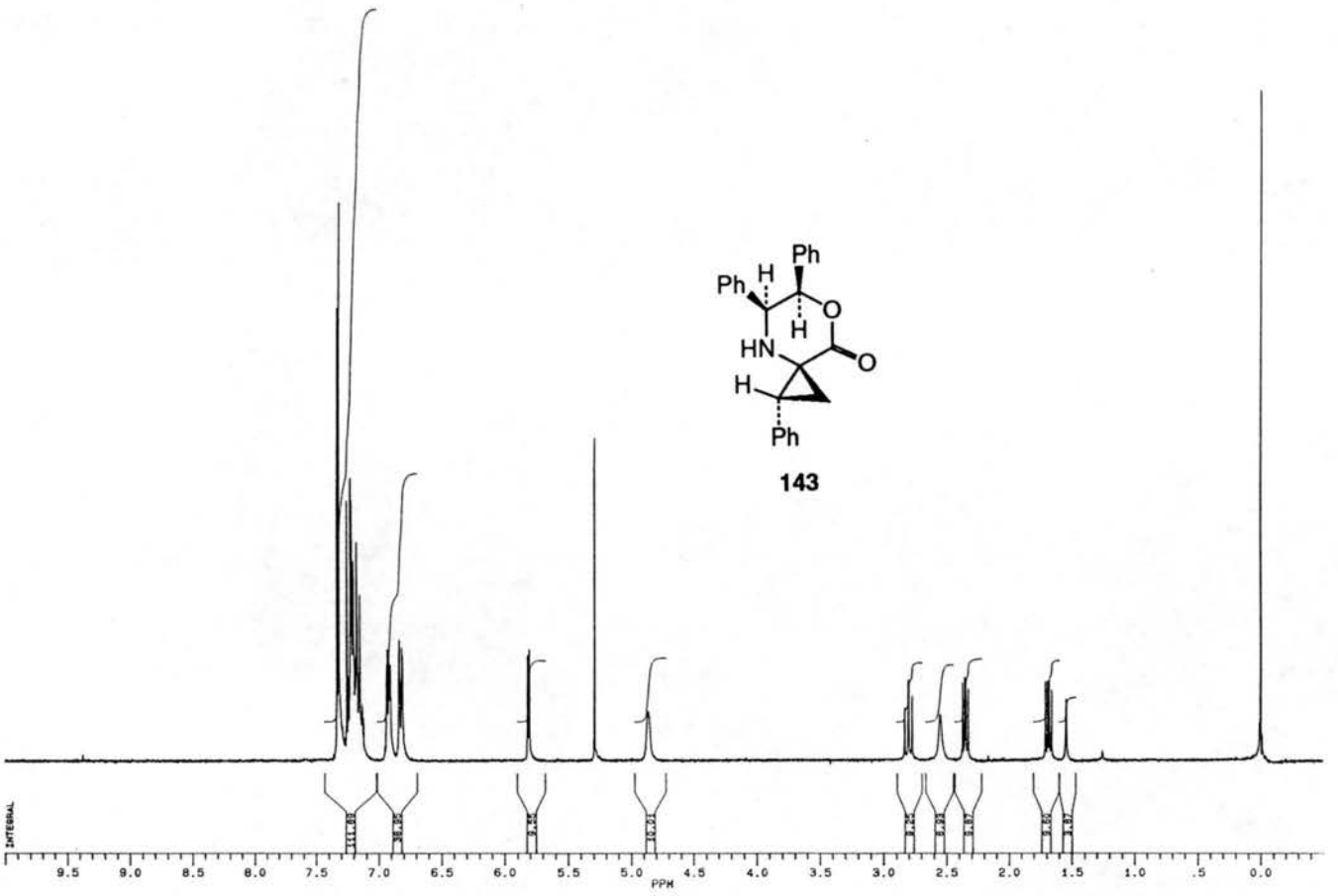
SEPF539.005
DATE 12-9-92

SF 282.408
SY 192.0
O1 11280.000
SI 32768
TD 32768
SW 29411.765
HZ/PT 1.795

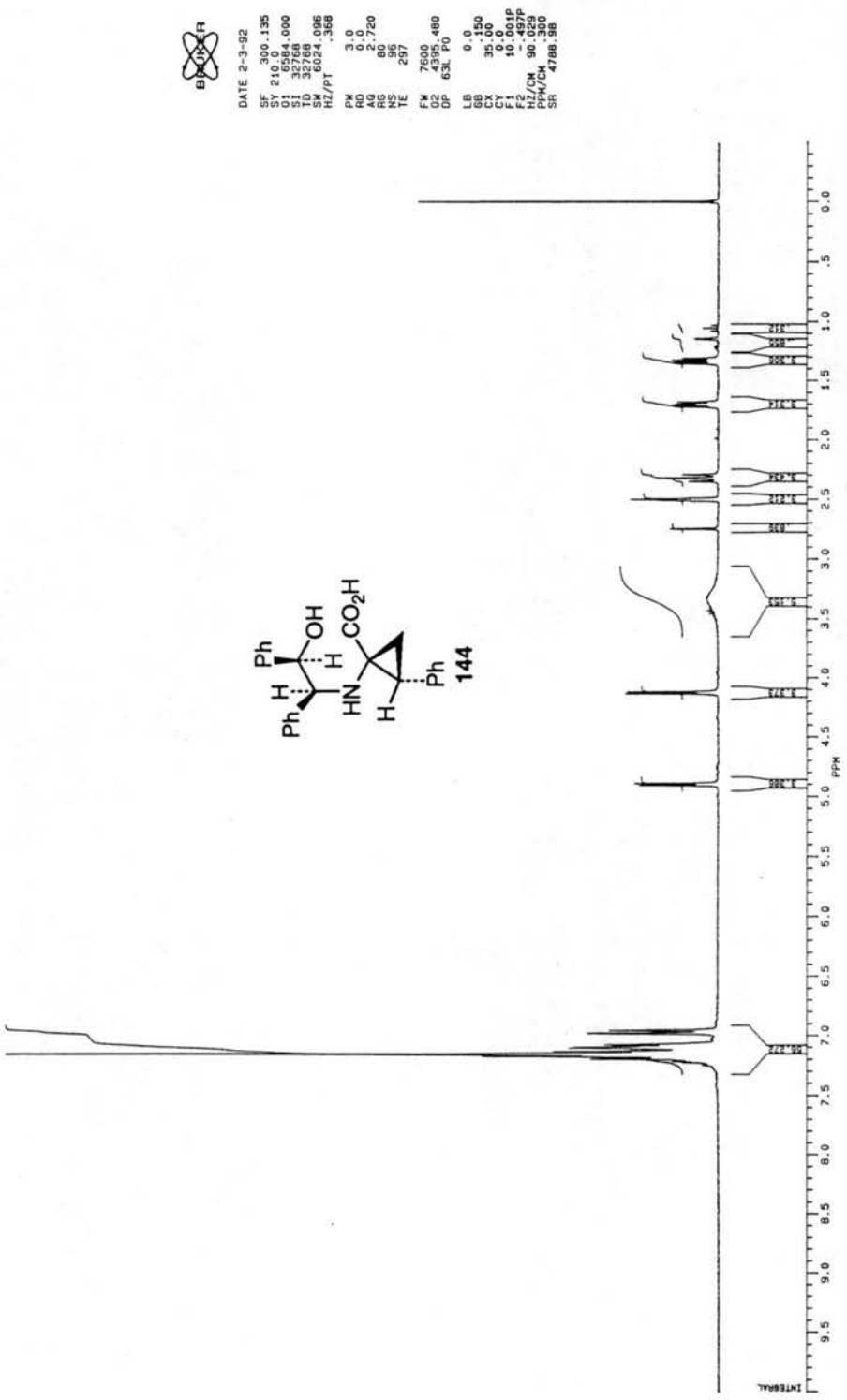
PW 3.0
RD 1.500
AQ .557
RG 20
NS 56
TE 297

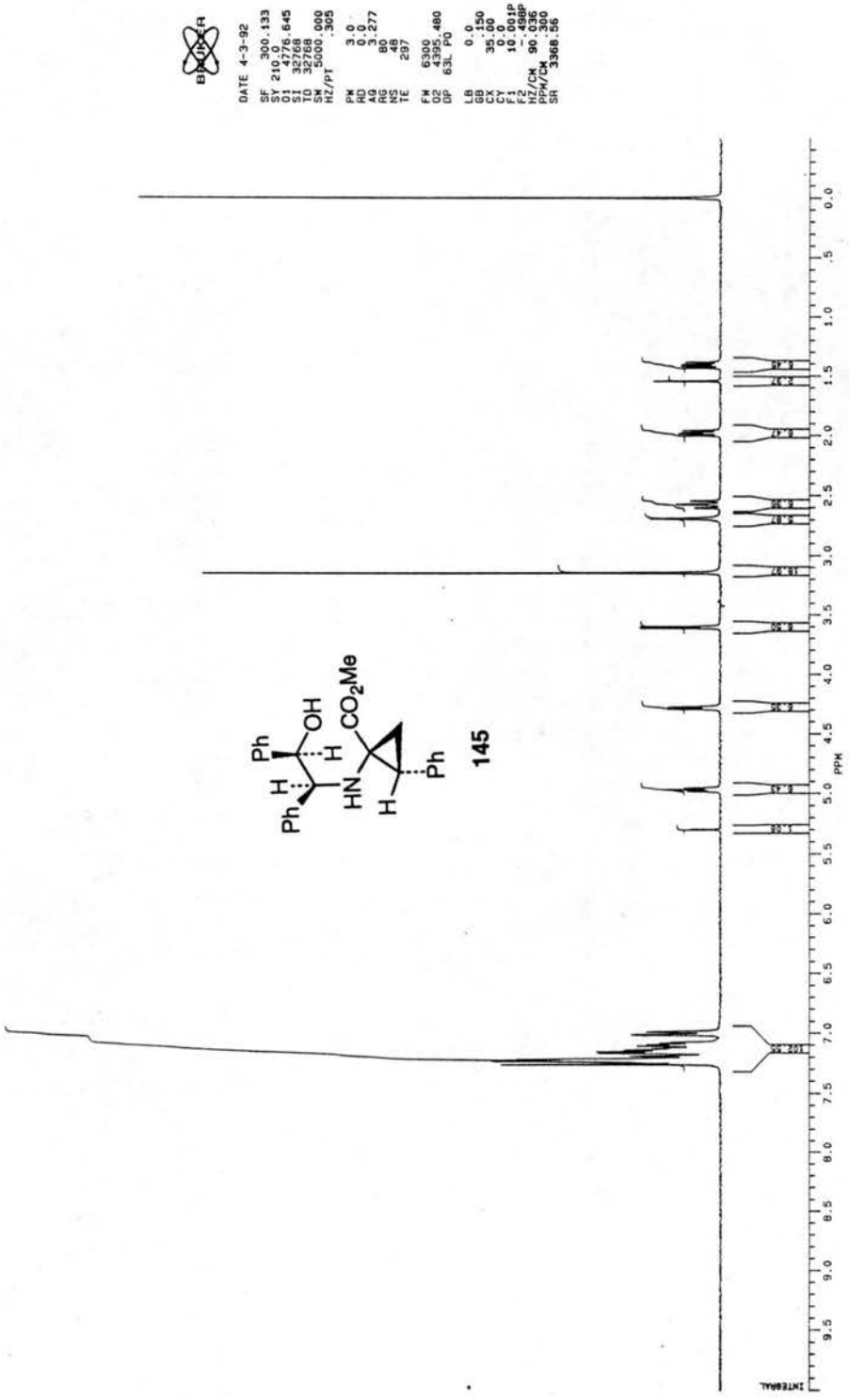
FW 36800
O2 4800.000
DP 63L PO

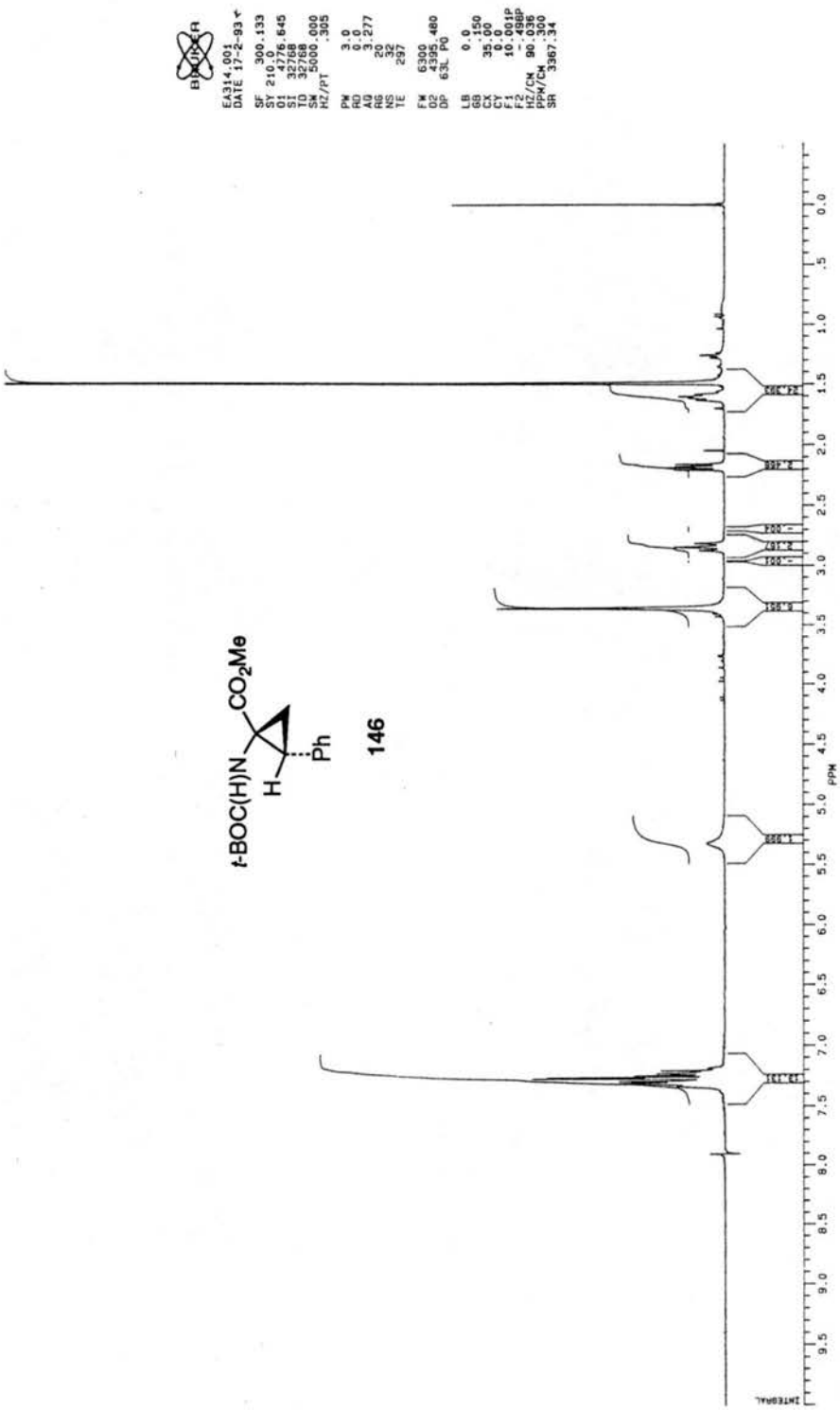
LB 0.0
GB 0.0
CX 35.00
CY 0.0
F1 -70.001P
F2 -84.996P
HZ/CM 120.993
PPM/CM .428
SR 21320.97

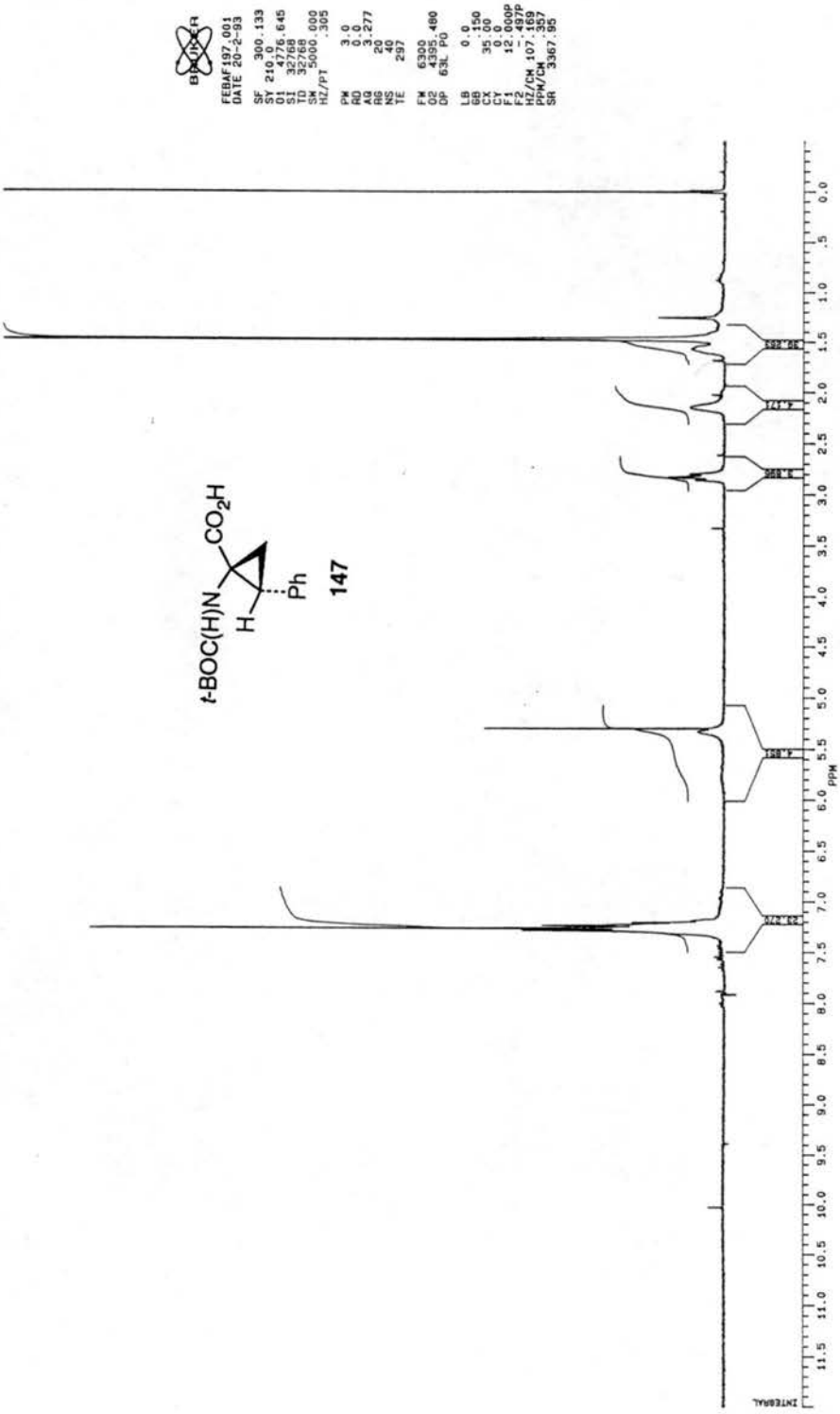

Ph
H
Ph
O
H
HN
O
H
Ph
143
INTEGRAL
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

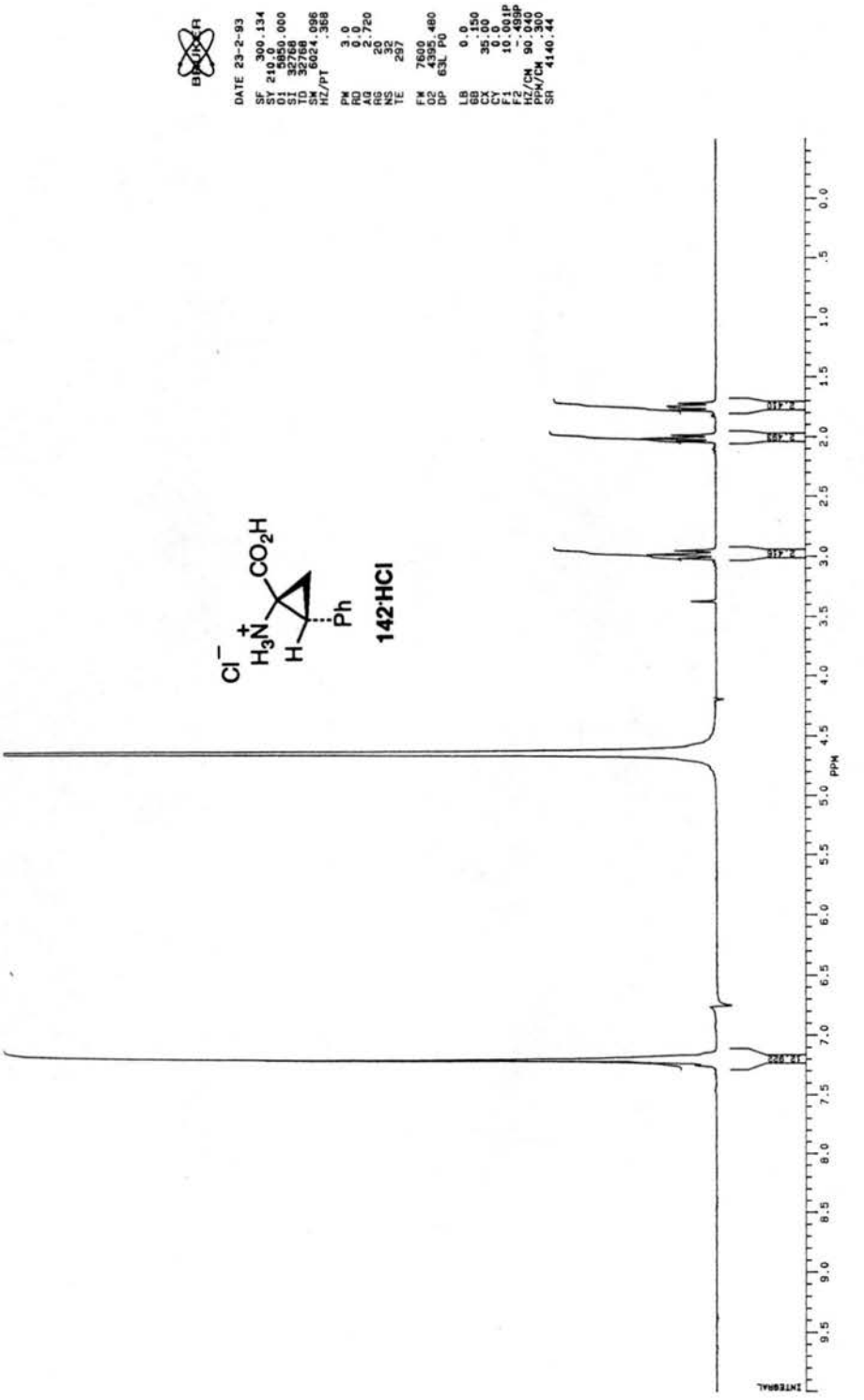
DATE 15-5-91
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 40
NS 8
TE 297
FW 6300
O2 4395.480
DP 63L DO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3369.17

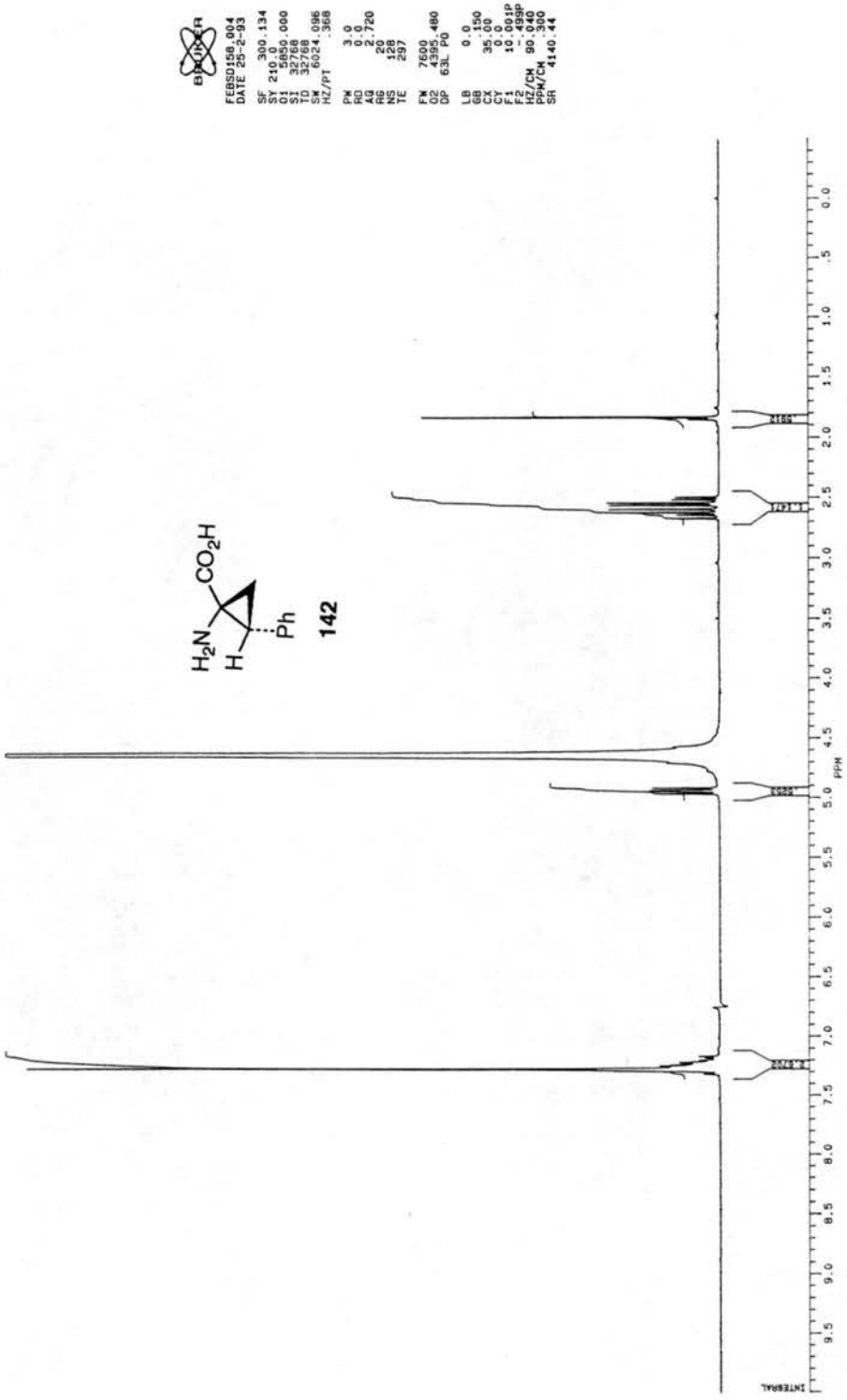

BRUKER
DATE 2-3-92
SF 300.135
SW 10.0
OI 6584.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AQ 2.720
NS 80
DS 96
TE 297
FW 7600
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
F1 0.0
F2 10.001P
HZ/CM .497P
PPM/CM 90.029
SR .300
4788.98
Ph
OH
H
CO2H
HN
Ph
H
Ph
H
144
INTEGRAL
PPM

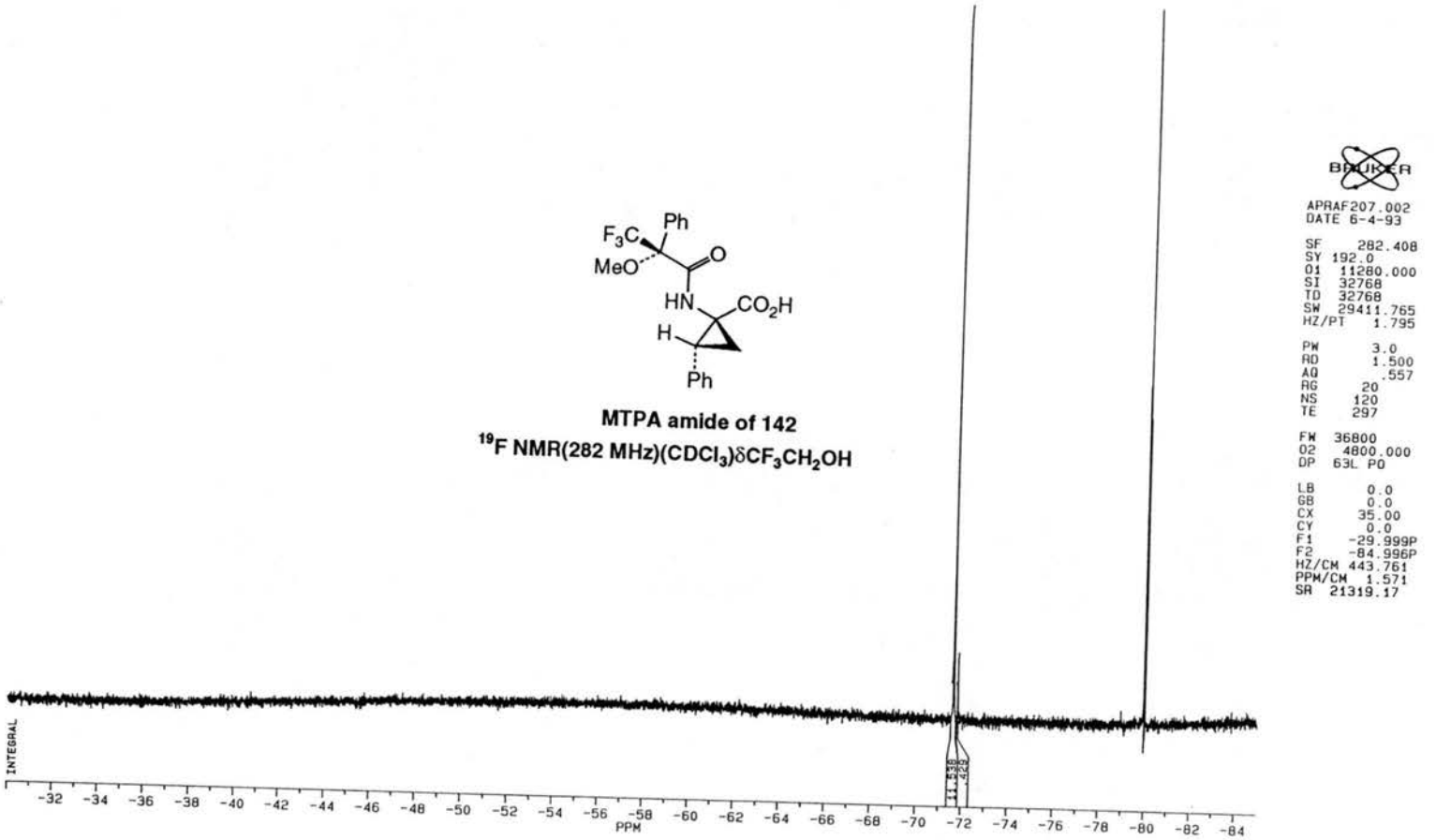

DATE 4-3-92
SF 300.133
SY 210.0
01 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 80
NS 48
TE 297
FW 6300
D2 4395.480
DP 63L PO
LB 0.0
GB 35.150
CX 0.0
CY 10.001P
F1 -.498P
F2 90.936
PPM/CM 300
SR 3368.56
Ph
OH
H
CO2Me
HN
H
Ph
H
Ph
145
PPM


t-BOC(H)N
CO2Me
H
Ph
146
EA314.001
DATE 17-2-93
SF 300.133
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
AQ 3.277
RG 20
NS 32
TE 297
FW 6300
O2 4395.480
DP
LB .150
GB
CX 35.00
CY 0.0
F1 10.001P
F2 -.488P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
PPM


t-BOC(H)N
CO2H
H
Ph
147
PPM

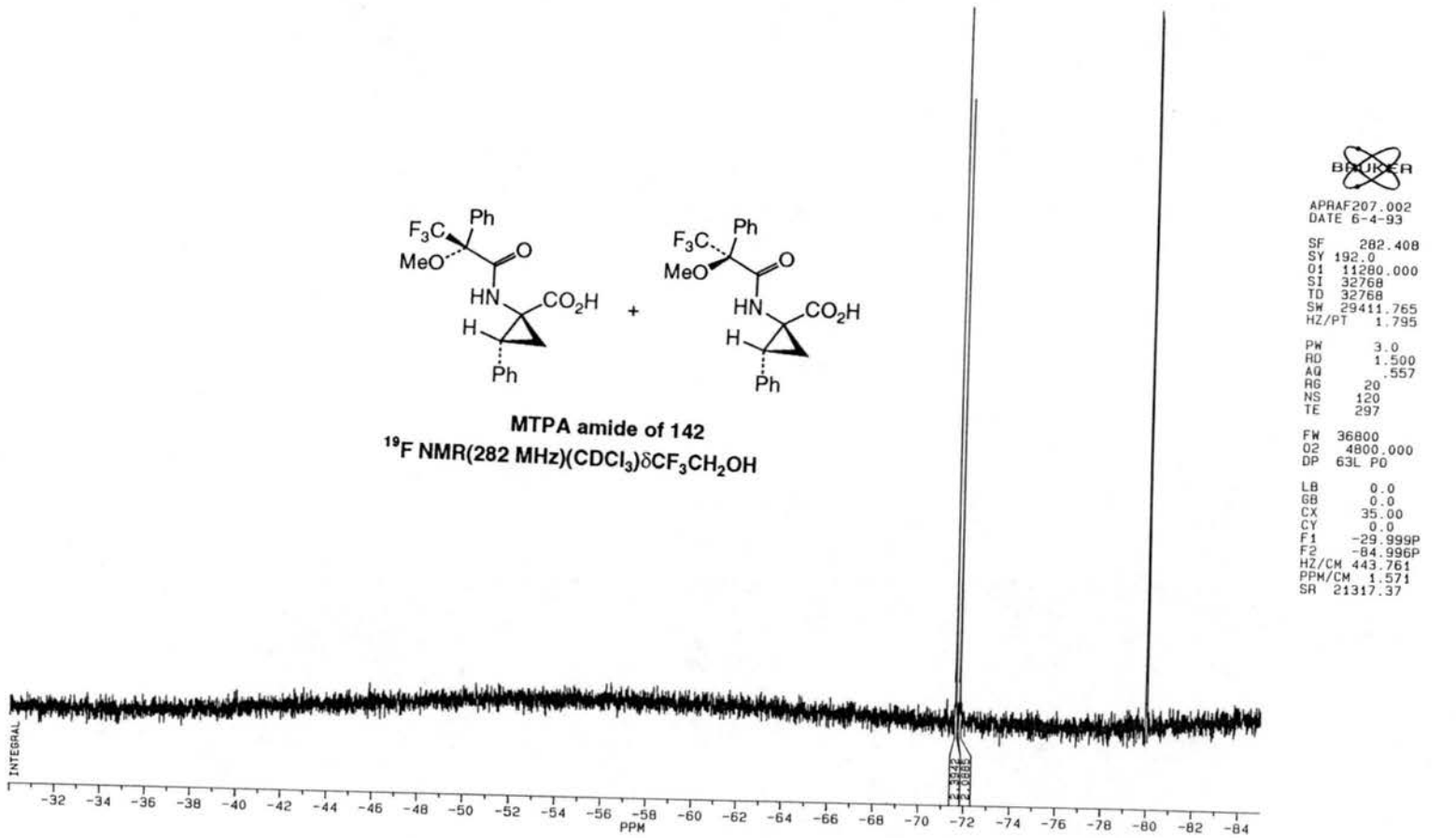

BRUKER
DATE 23-2-93
SF 300.134
SY 210.0
O1 5850.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0
AQ 2.720
RG 20
NS 32
TE 297
FW 7600
O2 4395.480
DP 63L PO
LB 0.0
GB .150
LX 35.00
CY 0.0
F1 10.0019P
F2 -.499P
PW/CM 90.000
PW1/CM 90.000
SR 4140.44
Cl^-
H_3N^+
CO_2H
Ph
H
142·HCl
INTEGRAL
PPM


FEBS0150.004
DATE 25-2-93
SF 300.134
SY 210.00
01 5850.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AG 2.720
RG 20
NS 128
TE 297
FW 7600
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -499P
HZ/CM 90.040
PPM/CM .300
SR 4140.44
INTEGRAL
PPM
H2N
CO2H
H
Ph
142



MTPA amide of 142

^{19}F NMR(282 MHz)($CDCl_3$)δCF_3CH_2OH



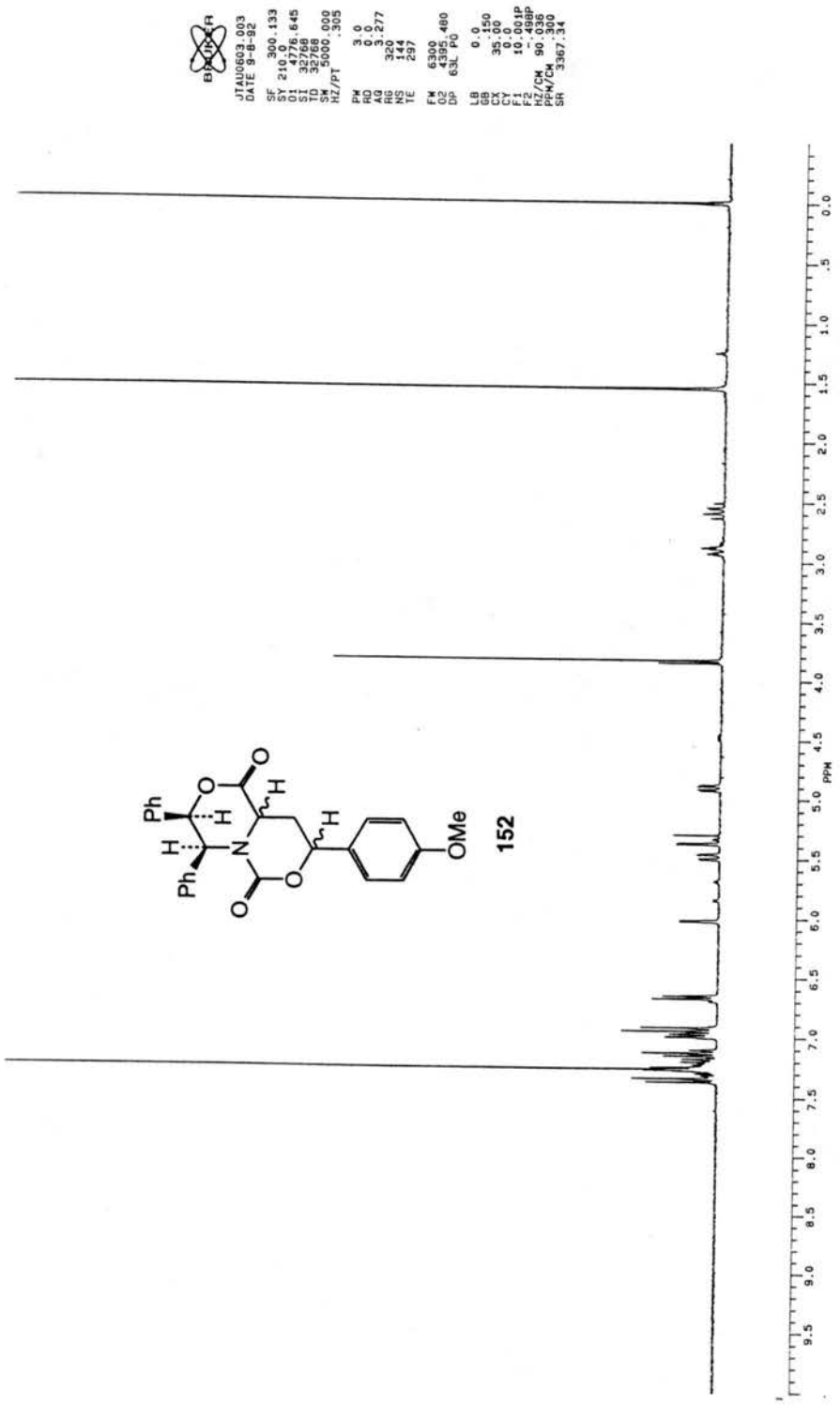
MTPA amide of 142

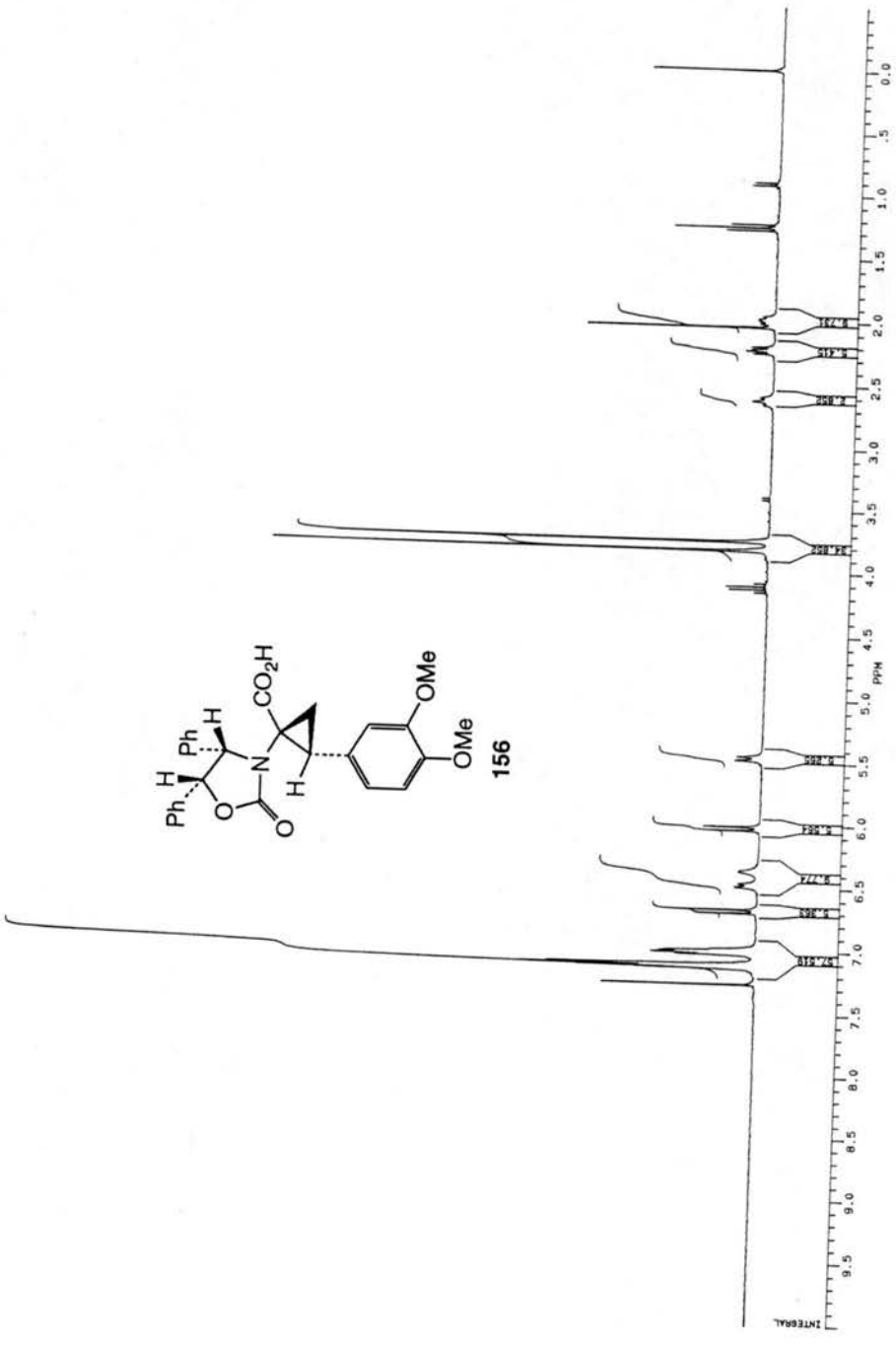
^{19}F NMR(282 MHz)($CDCl_3$)δCF_3CH_2OH

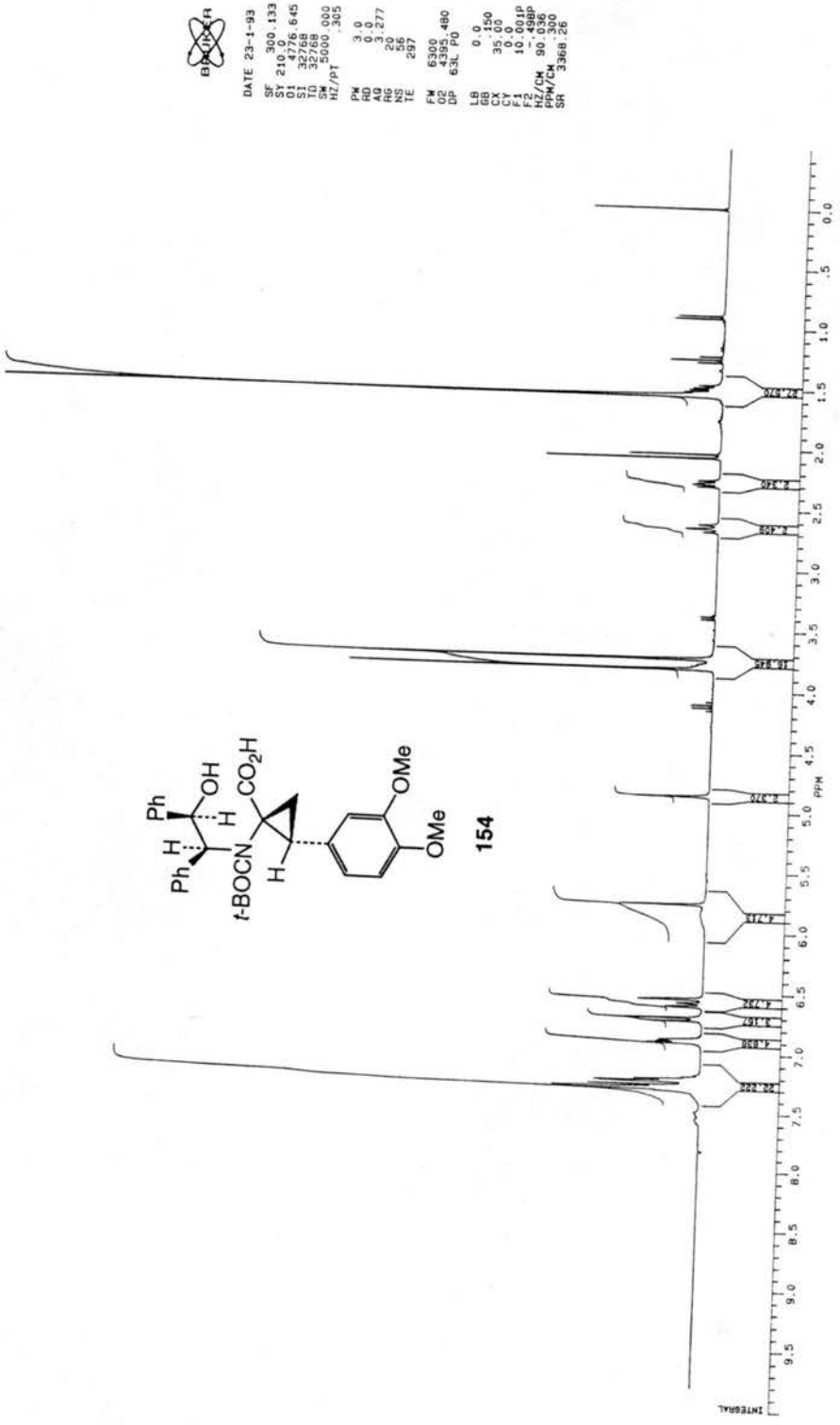
BRUKER

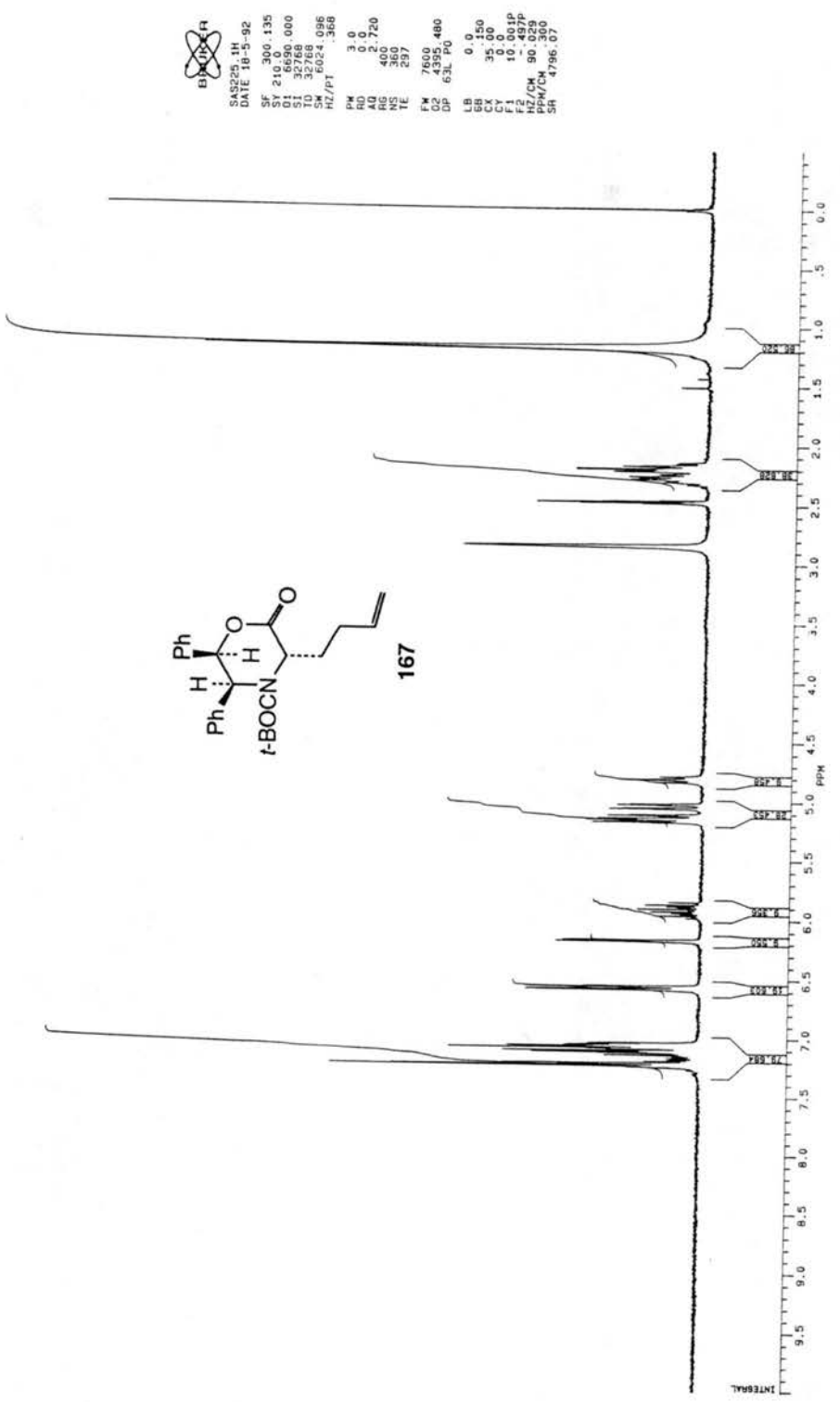
APRAF207.002
DATE 6-4-93

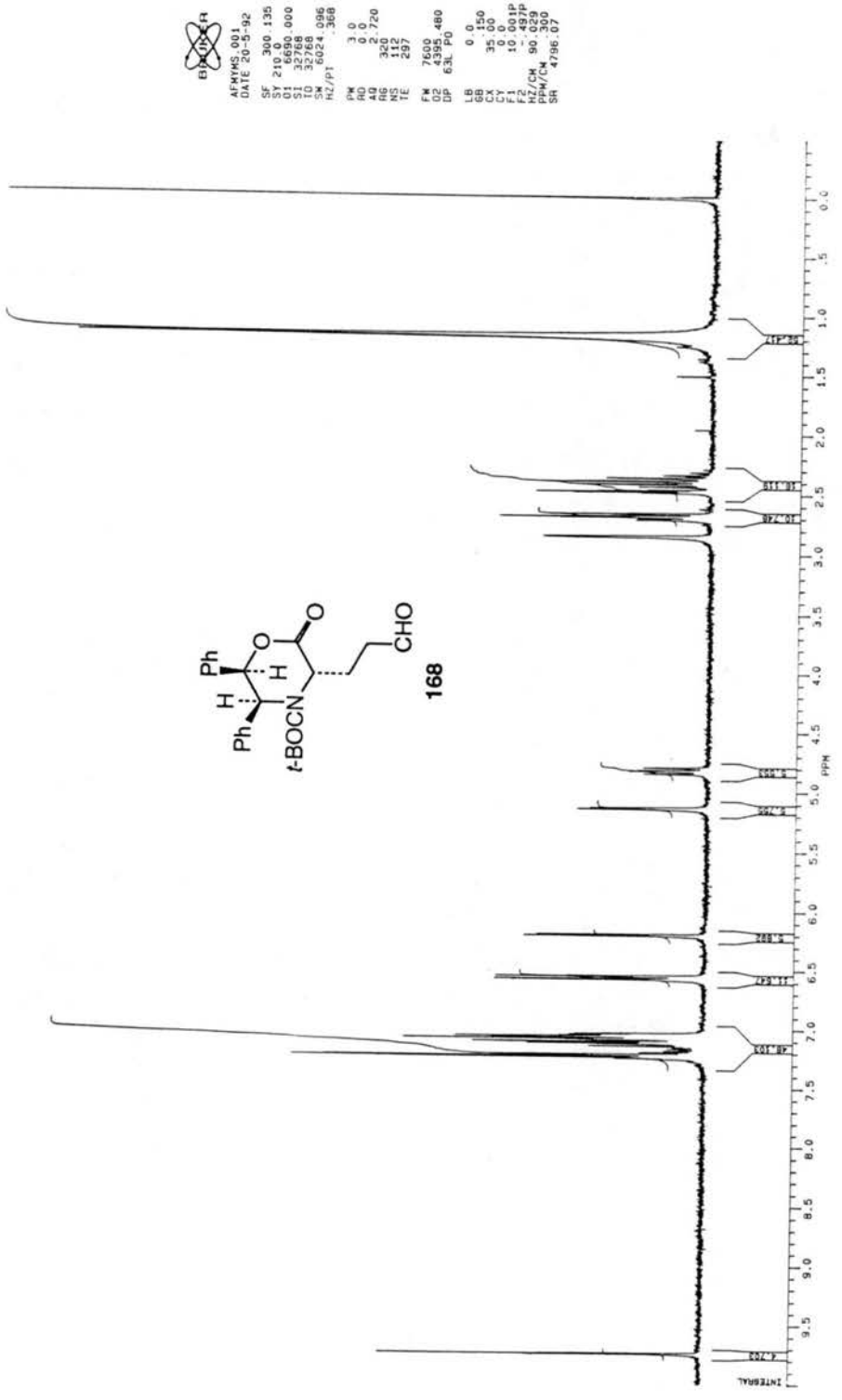
SF	282.408
SY	192.0
O1	11280.000
SI	32768
TD	32768
SW	29411.765
HZ/PT	1.795
PW	3.0
RD	1.500
AQ	.557
RG	20
NS	120
TE	297
FW	36800
O2	4800.000
DP	63L P0
LB	0.0
GB	0.0
CX	35.00
CY	0.0
F1	-29.999P
F2	-84.996P
HZ/CM	443.761
PPM/CM	1.571
SR	21317.37

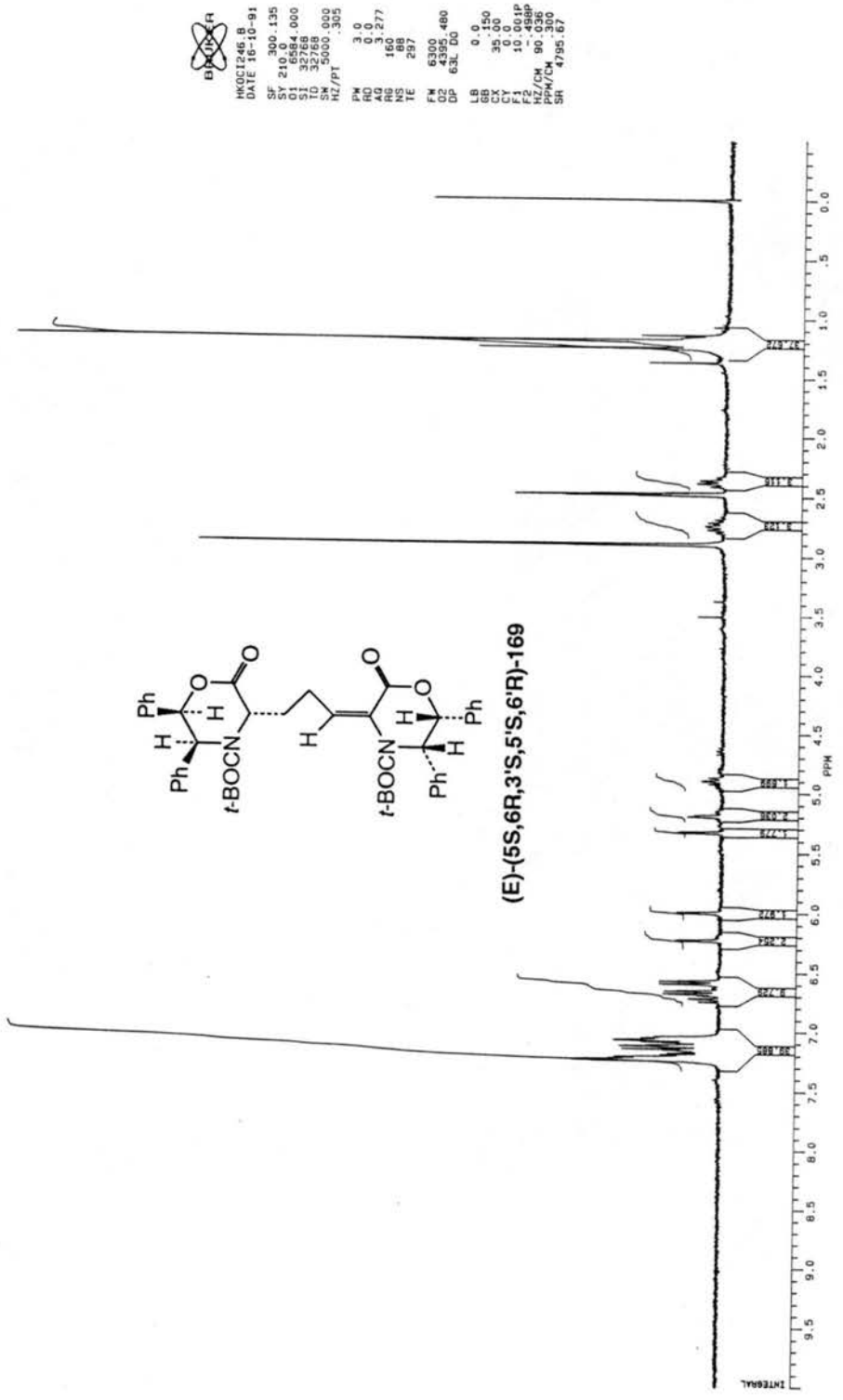

JTAU0603.003
DATE 9-8-92
SF 300.133
SY 210.79
D1 2.778645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 320
NS 144
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 .498P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
Ph
H
O
H
H
N
Ph
O
O
H
OMe
152
PPM

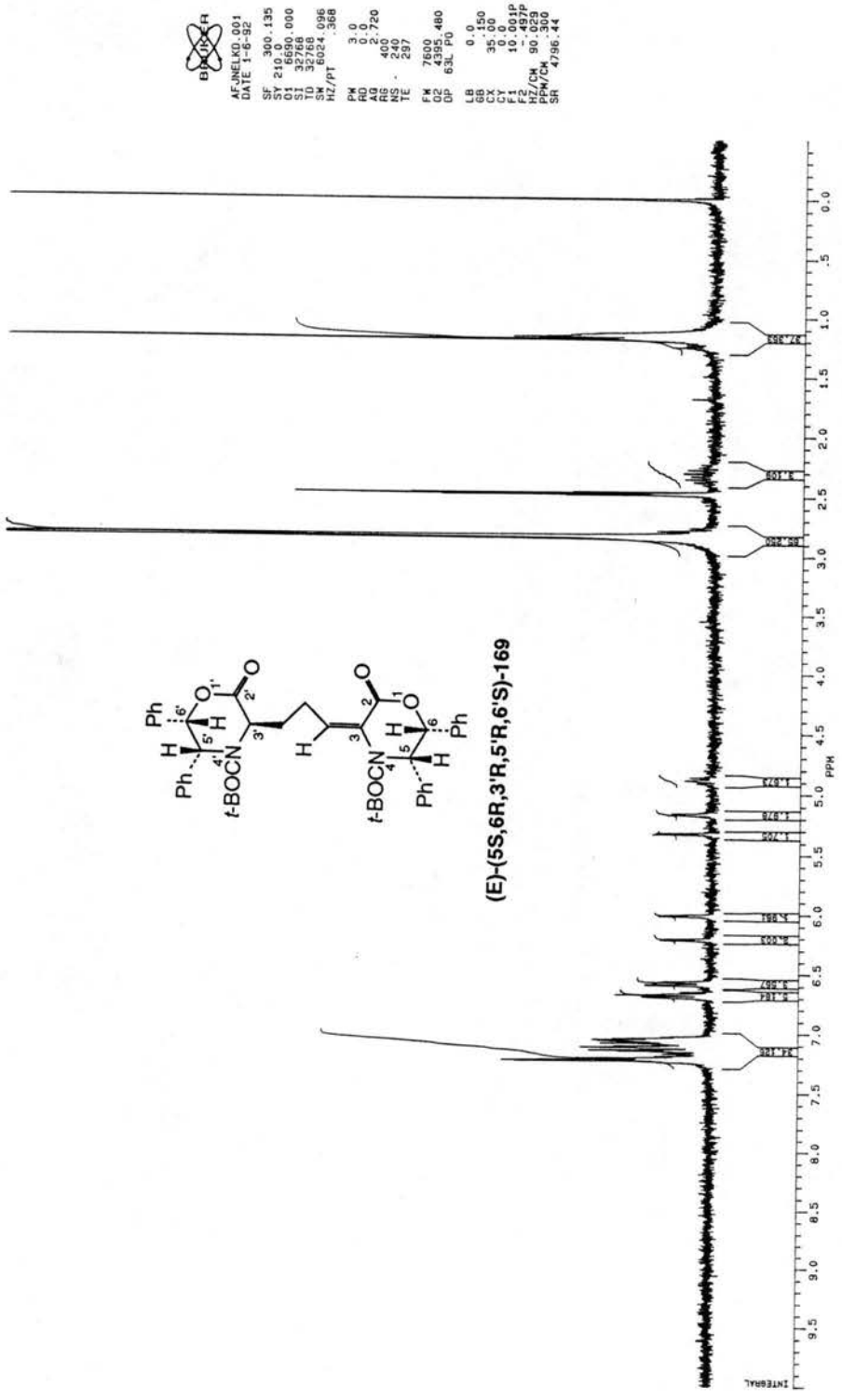

Ph
H
Ph
H
N
O
O
CO2H
H
OMe
OMe
156
PPM
INTEGRAL


Ph
OH
H
Ph
H
t-BOCN
CO2H
H
OMe
OMe
154
DATE 23-1-93
SF 300.133
SY 210.0
DI 276.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 56
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 .498P
HZ/CM 90.195
PPM/CM .300
SR 3368.26
PPM
INTEGRAL

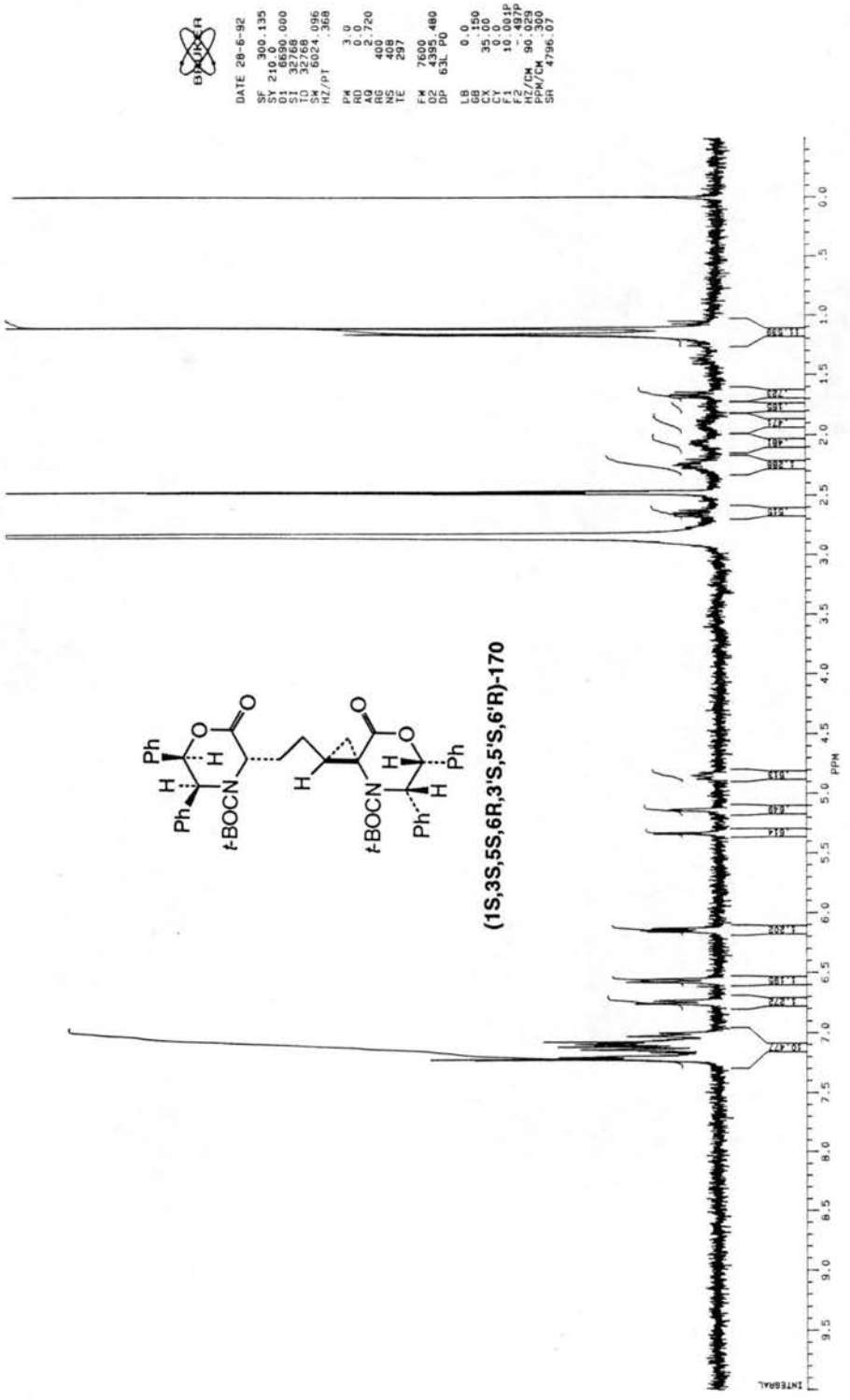

BRUKER
SAS225.1H
DATE 18-5-92
SF 300.135
SY 210.0
SI 6590.000
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0
AQ 2.720
RG 400
NS 360
TE 297
FW 7600
D2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 .497P
HZ/CM 90.429
PPM/CM 90.360
SA 4796.07
Ph
H
O
O
H
Ph
t-BOCN
167
PPM
INTEGRAL


AFMYMS.001
DATE 20-5-92
SF 300.135
SY 210.0
O1 6690.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0
AQ 2.720
RG 320
NS 112
TE 297
FW 7600
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.497P
HZ/CM 90.029
PPM/CM 13.300
SR 4796.07
Ph
H
O
O
H
Ph
t-BOCN
CHO
168
INTEGRAL
PPM

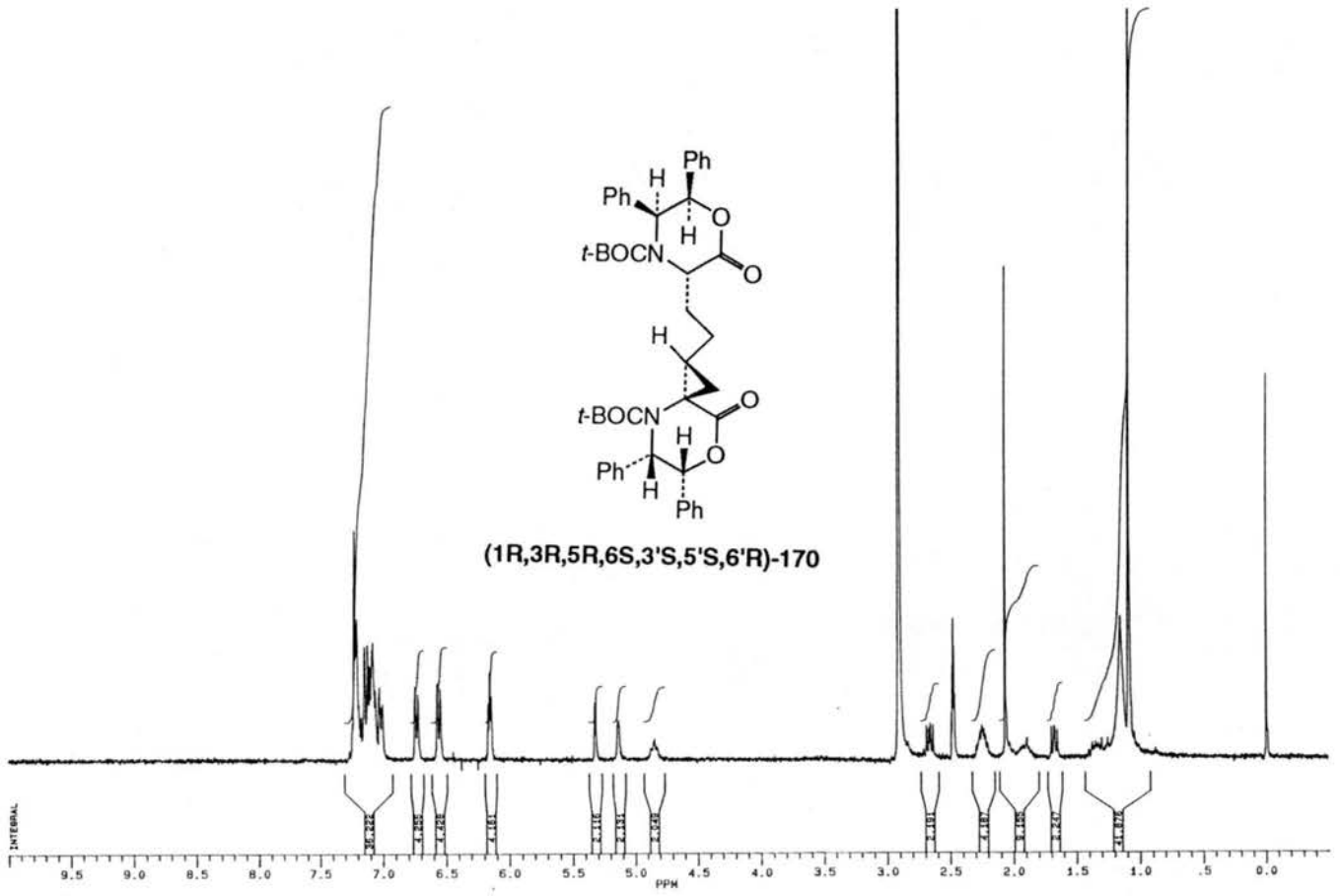

HKOCI246.8
DATE 16-10-91
SF 300.135
SY 210.0 6584.000
O1 32768
SI 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 160
NS 88
TE 297
FW 6300
D2 4395.480
DP 63L 00
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 4795.67
INTEGRAL
PPM
t-BOCN
Ph
(E)-(5S,6R,3'S,5'S,6'R)-169



(E)-(5S,6R,3'R,5'R,6'S)-169



(1S,3S,5S,6R,3'S,5'S,6'R)-170



(1R,3R,5R,6S,3'S,5'S,6'R)-170

BRUKER

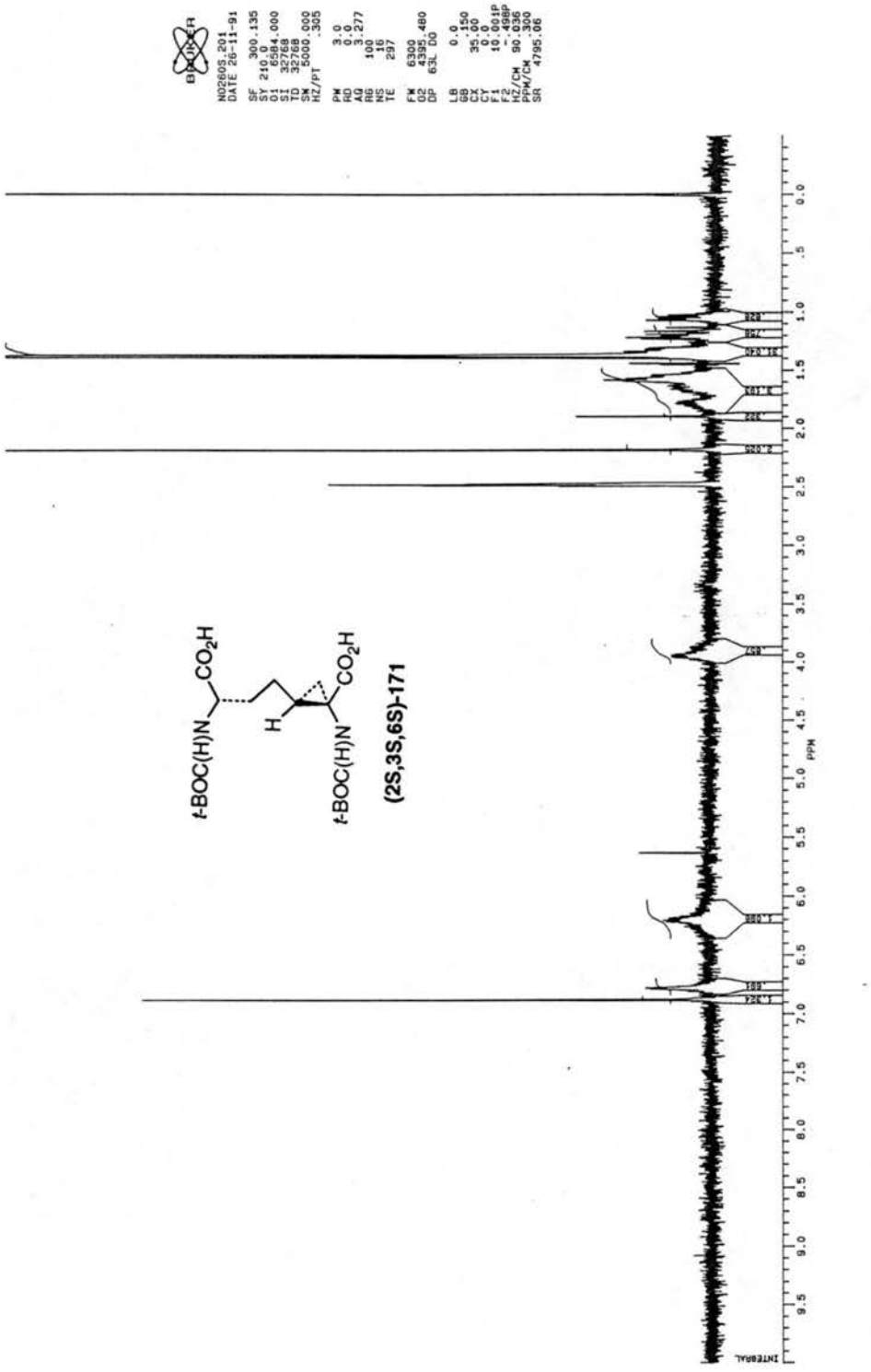
A.001
DATE 12-8-92

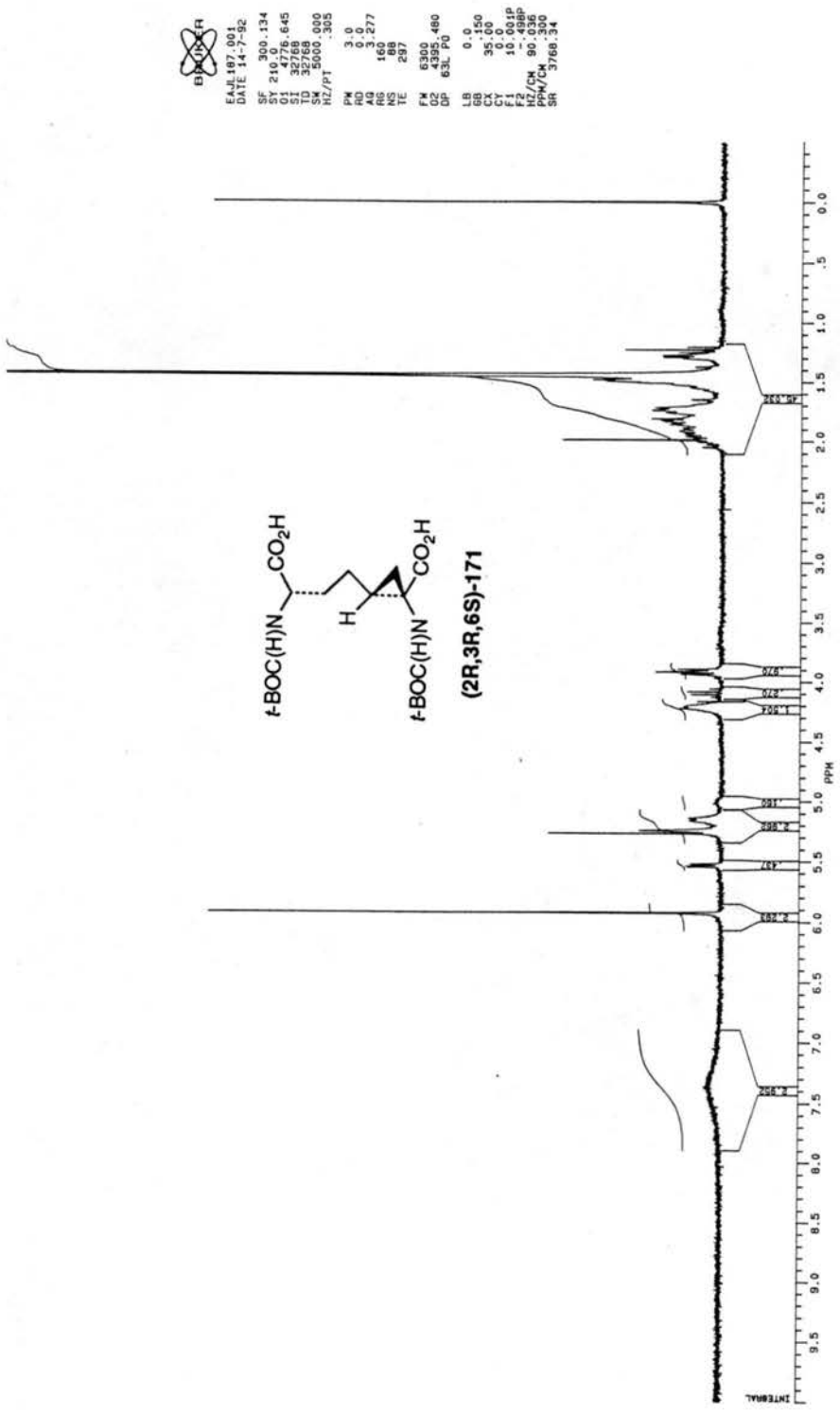
SF 300.135
SY 210.0
O1 6690.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368

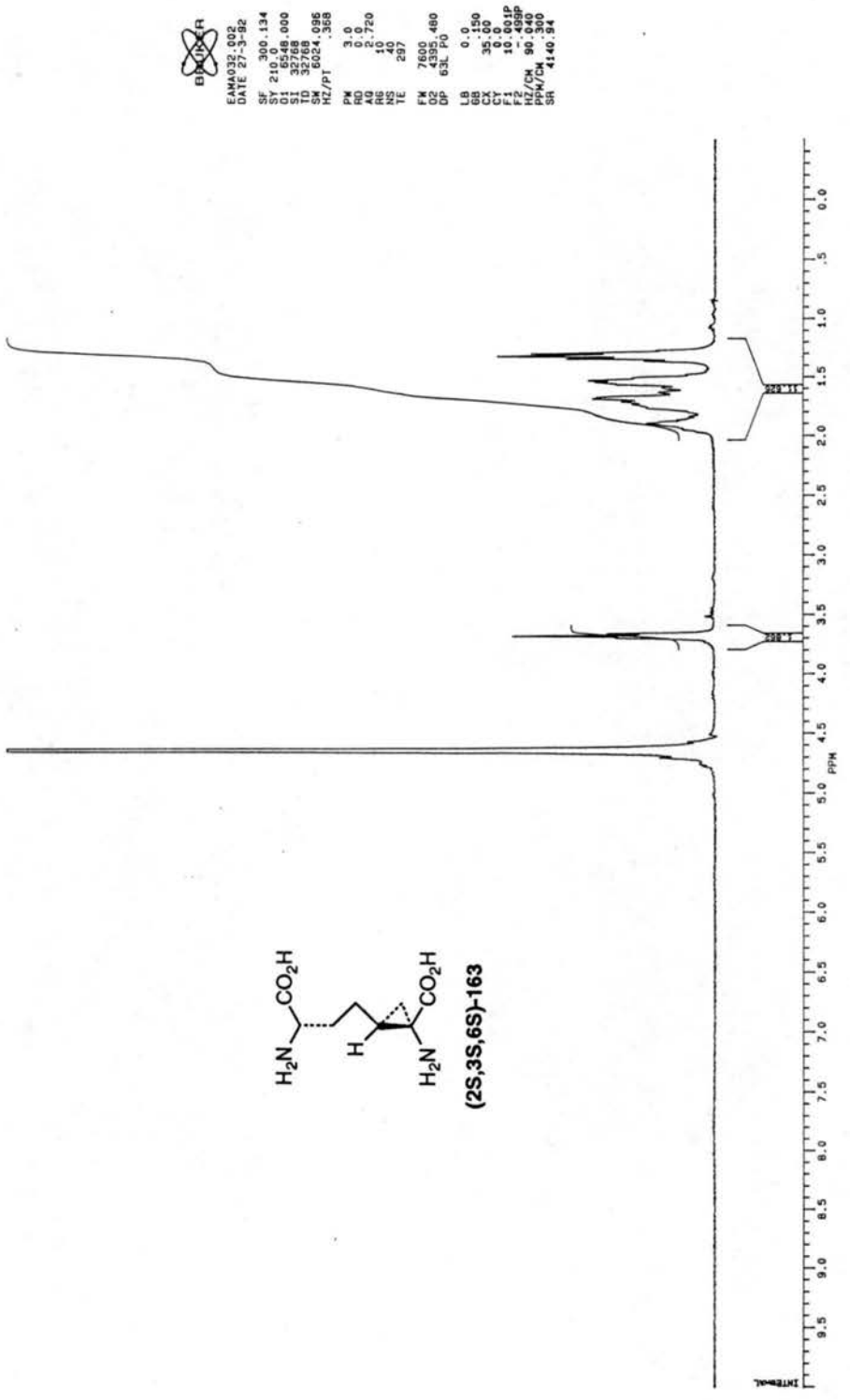
PW 3.0
RD 0.0
AQ 2.720
RG 320
NS 192
TE 297

FW 7600
O2 4395.480
DP 63L PO

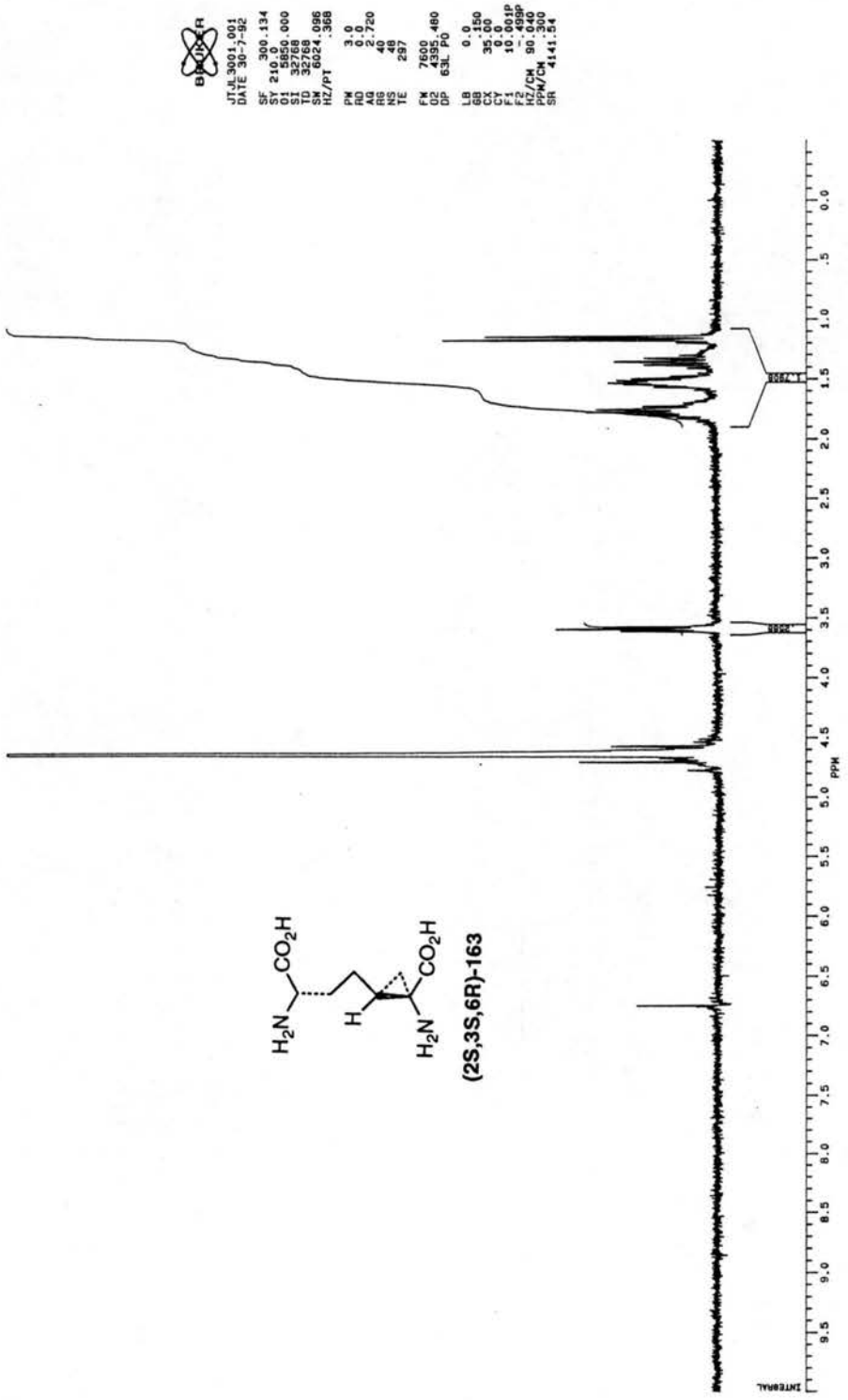
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.497P
HZ/CM 90.029
PPM/CM .300
SR 4795.34

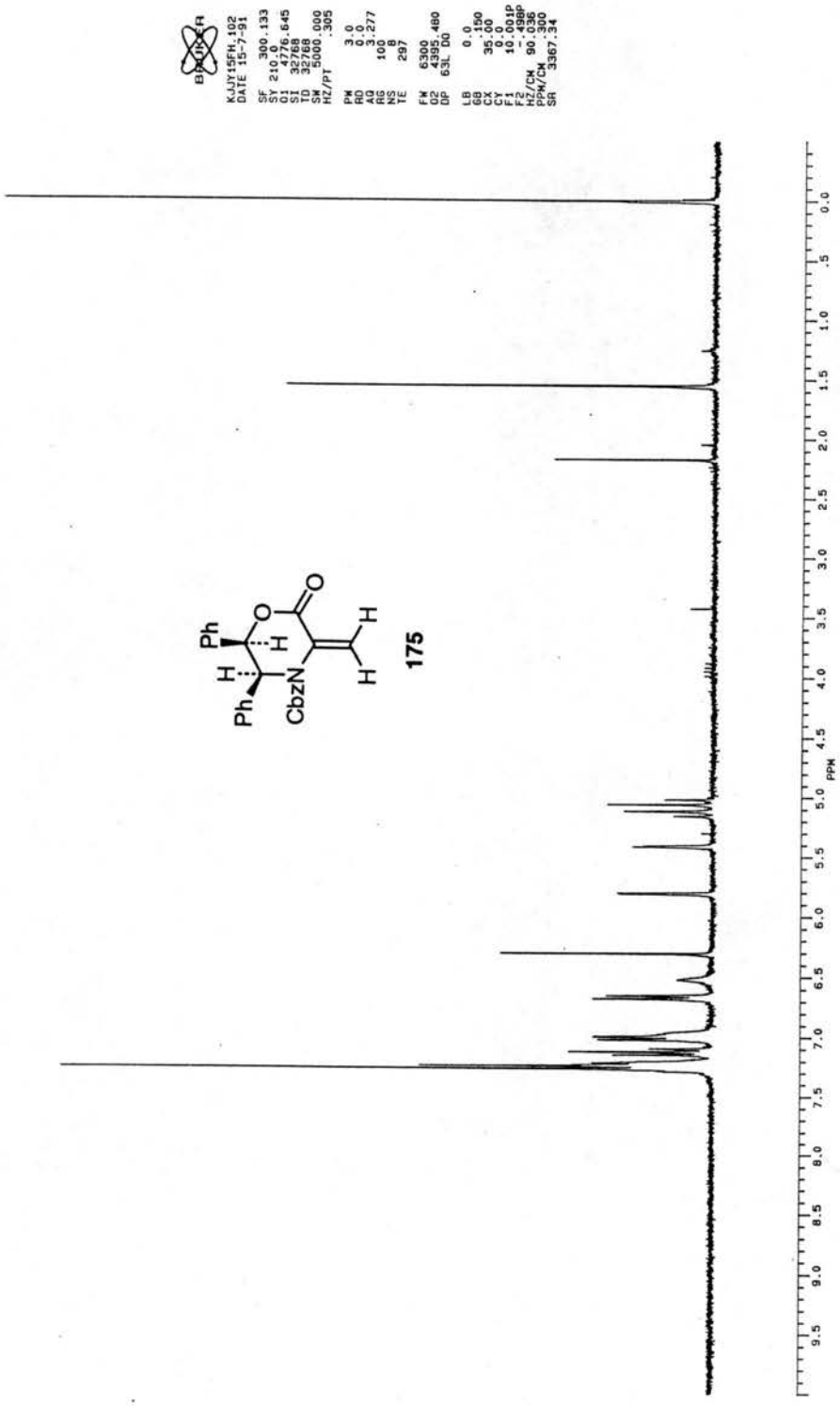

t-BOC(H)N
CO2H
H
t-BOC(H)N
CO2H
(2S,3S,6S)-171
PPM
INTEGRAL

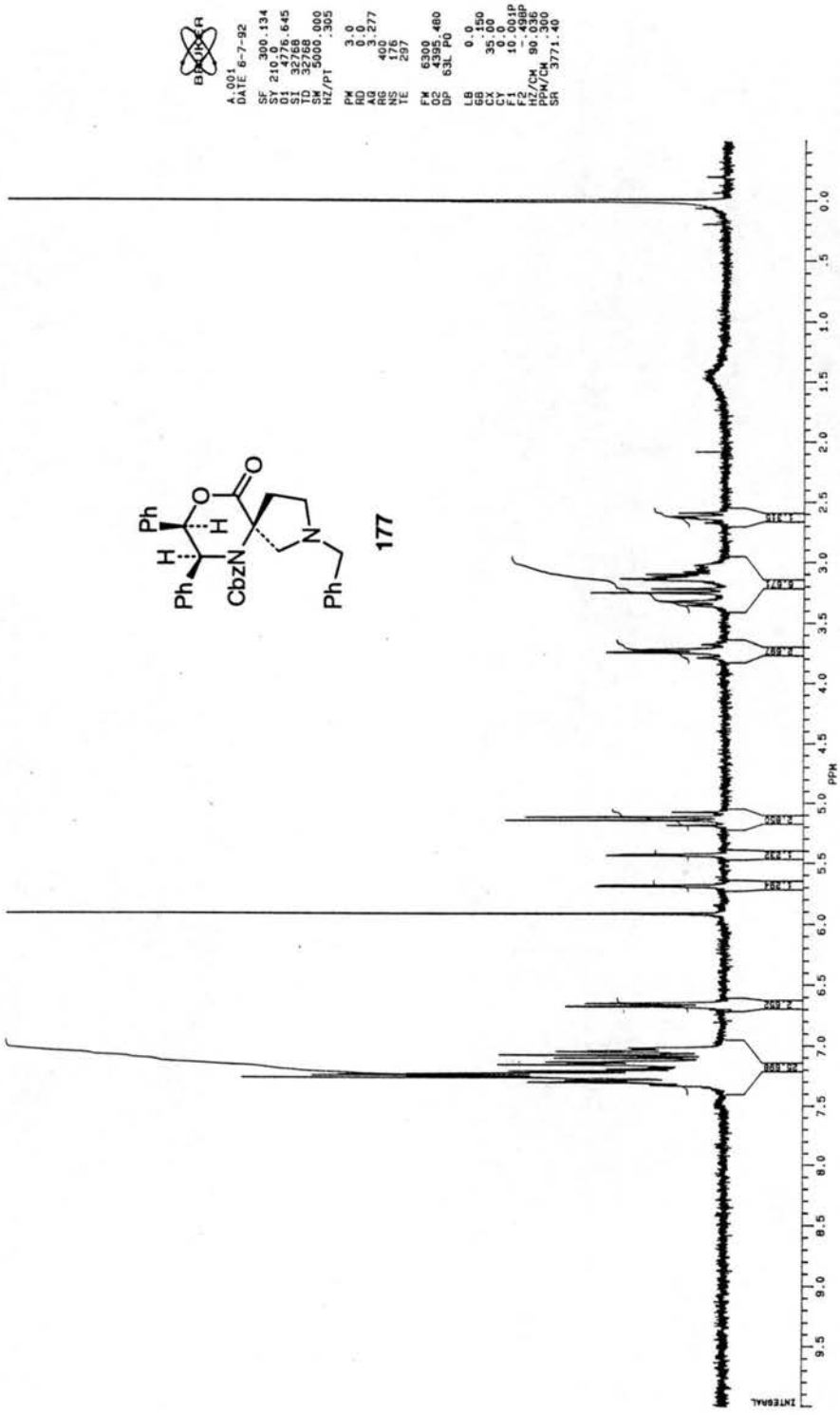

EAJL107.001
DATE 14-7-92
SF 300.134
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 160
NS 88
TE 297
FW 6300
O2 4395.480
DP 63L P0
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3768.34
t-BOC(H)N
CO2H
H
t-BOC(H)N
CO2H
(2R,3R,6S)-171
PPM
INTEGRAL

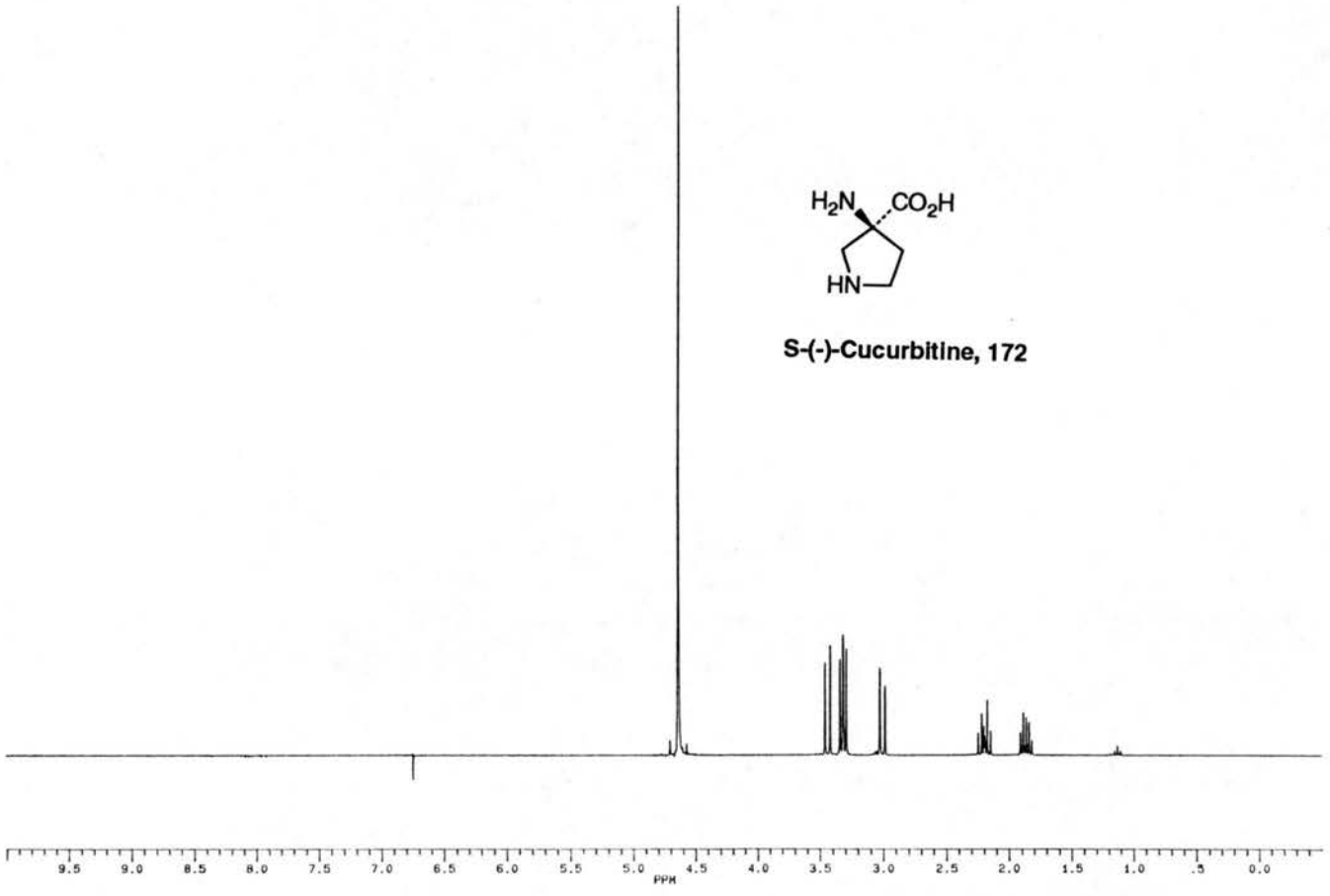


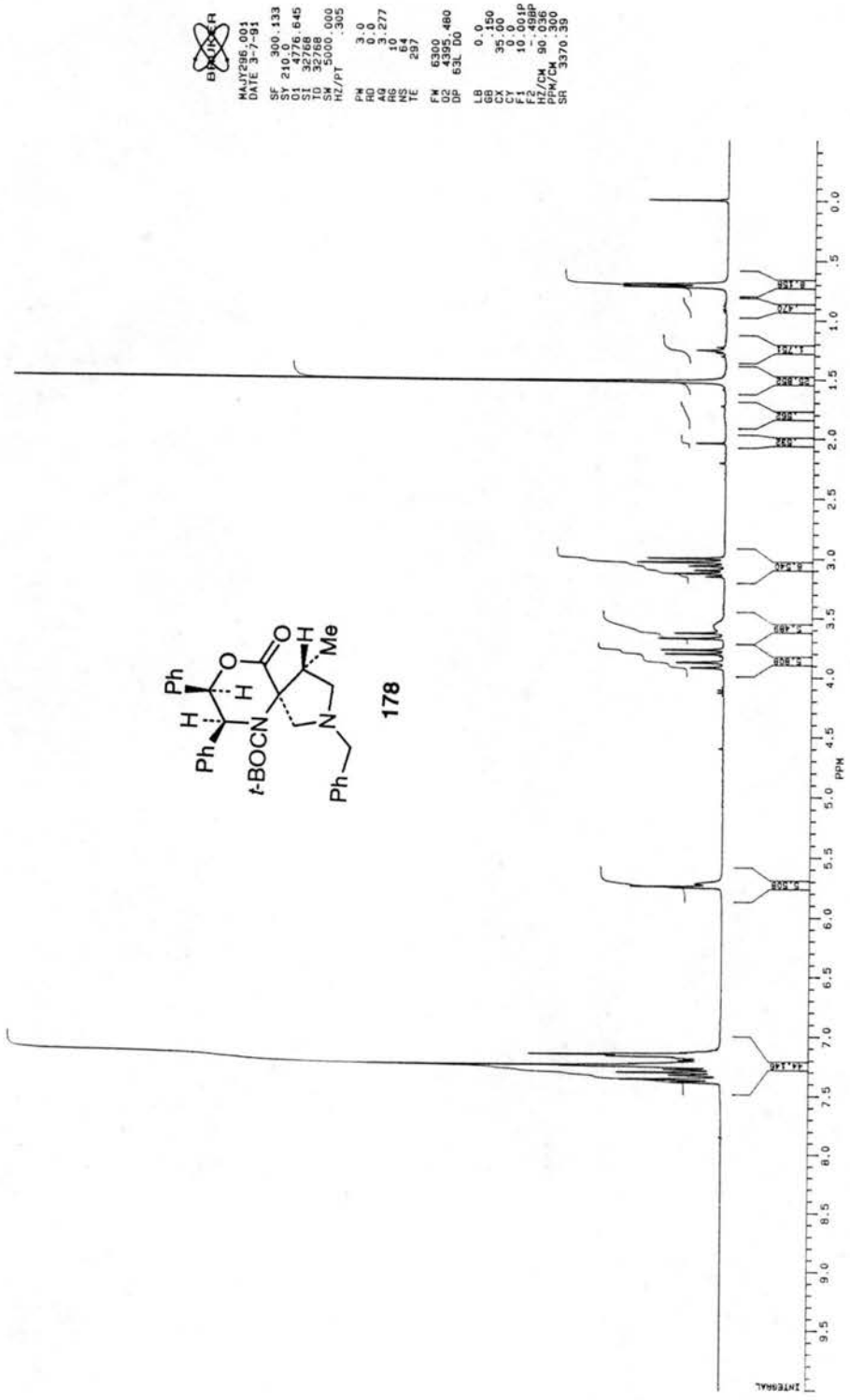
(2S,3S,6S)-163


JTJL3001.001
DATE 30-7-92
SF 300.134
SY 210.0
SI 15960.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AG 2.720
RG 40
NS 48
TE 297
FW 7600
D2 4395.480
DP 63L PO
LB .0
GB .150
CX 35.00
CY 0.0
F1 10.0018P
F2 -.4688P
HZ/CM 90.040
PPM/CM .300
SR 4141.54
PPM
INTEGRAL
H_2N
CO_2H
H
H_2N
CO_2H
(2S,3S,6R)-163


KJJY15FH.102
DATE 15-7-91
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 100
NS 8
TE 297
FW 6300
O2 4395.480
DP 63L DD
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3367.34
Ph
H
Ph
O
H
CbzN
O
H
H
175
PPM

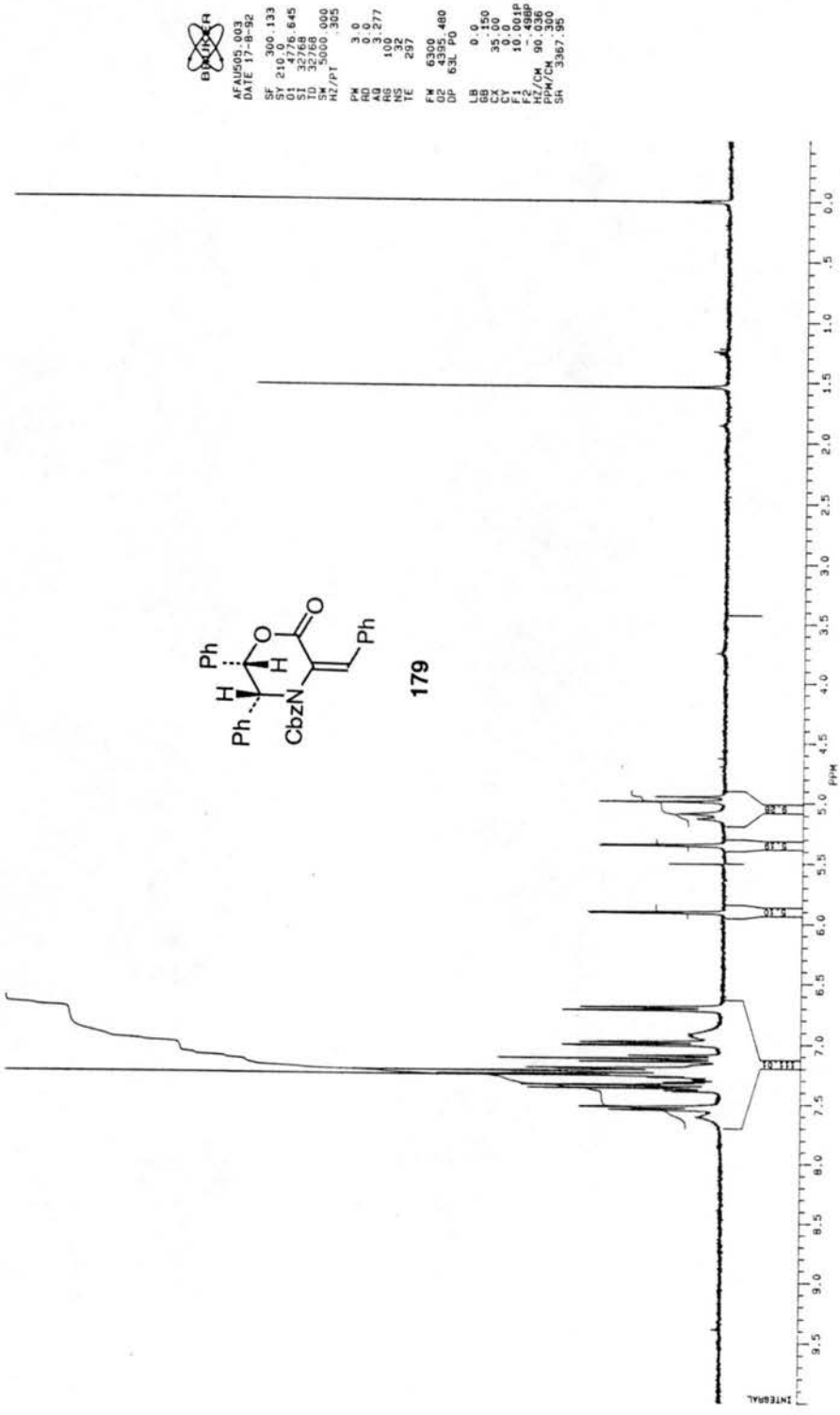

177
Ph
H
O
H
Ph
CbzN
Ph
PPM

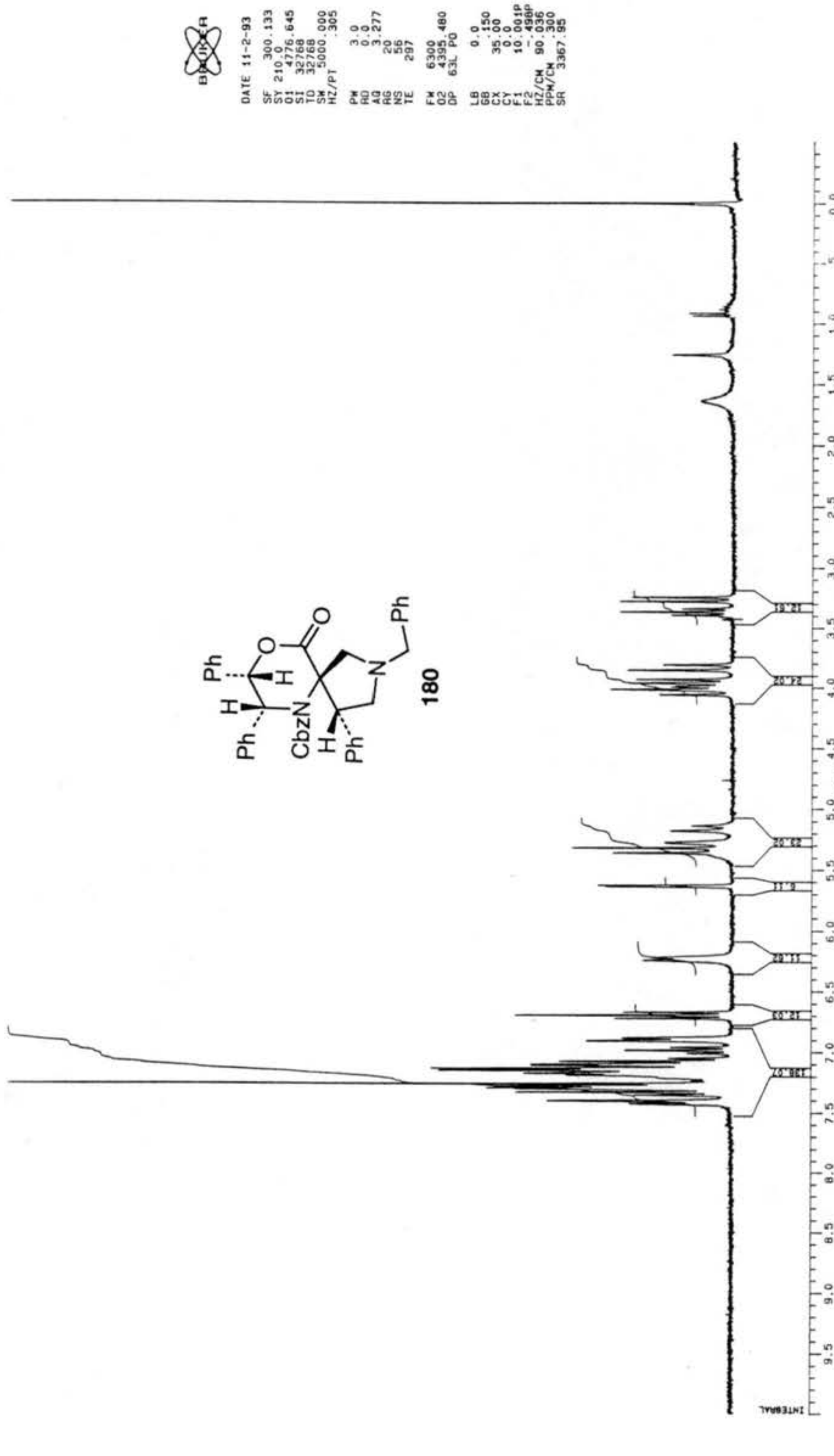

H2N
CO2H
HN
S-(-)-Cucurbitine, 172
BRUKER
DATE 11-9-92
SF 300.134
SY 210.0
O1 5850.000
SI 32768
TD 32768
SW 6024.096
HZ/PT .368
PW 3.0
RD 0.0
AQ 2.720
RG 10
NS 32
TE 297
FW 7600
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.499P
HZ/CM 90.040
PPM/CM .300
SR 4141.54
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

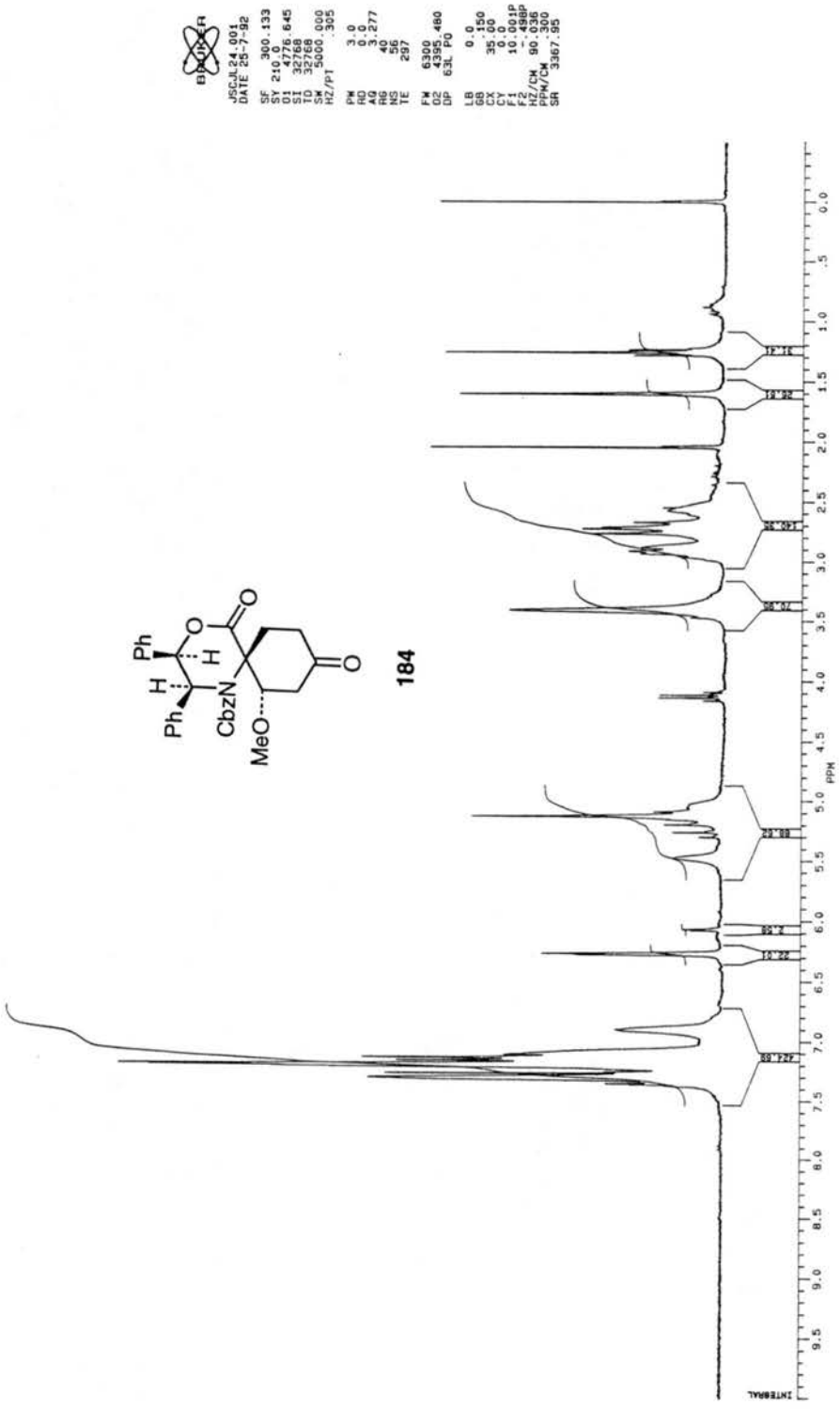

MAJY296.001
DATE 3-7-91
SF 300.133
SY 210.0
01 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 10
NS 64
TE 297
FW 6300
D2 4.395480
DP 63L.00
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3370.39
PPM
INTEGRAL

Ph
H
O
H
Ph
t-BOCN
O
H
Me
N
N
Ph

178


AFAU505.003
DATE 17-8-92
SF 300.133
SY 210.0
O1 1776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 100
NS 32
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 .498P
HZ/CM 90.036
PPM/CM .300
SW 3367.95
Ph
H
Ph
O
H
O
CbzN
Ph
179
INTEGRAL
PPM


DATE 11-2-93
SF 300.133
SY 210.0
O1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 56
TE 297
FW 6300
O2 4395.480
DP 63L PO
LB 0.0
GB .150
CX 35.00
CY 0.0
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SR 3367.95
Ph
H
Ph
O
O
CbzN
H
N
Ph
H
Ph
180
PPM
INTEGRAL


JSCJL24.001
DATE 25-7-92
SF 300.133
SY 210.0
D1 4776.645
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 40
NS 56
TE 297
FW 6300
D2 4395.480
DP 63L PG
LB 0.0
GB .150
CX 35.00
CY 0.00
F1 10.001P
F2 -.498P
HZ/CM 90.036
PPM/CM .300
SW 3367.95
Ph
H
O
O
H
Ph
CbzN
MeO
O
O
184
INTEGRAL
PPM

3.3 X-ray crystal structure data tables for 126b, 126f, 126a, and 132.

Compound 126b: See ORTEP drawing on page 209.

Table 1. Atomic coordinates (x 10^4) and isotropic thermal parameters ($Å^2$ x 10^3) for **126b**.

atom	x	y	z	U
C(1)	0.8786(5)	-0.1163(5)	0.6570(3)	24(1)*
C(4)	0.8898(5)	0.0355(5)	0.6945(4)	27(1)*
C(2)	0.9574(5)	-0.1649(6)	0.5828(3)	27(1)*
C(3)	1.0614(6)	-0.0819(6)	0.5249(4)	34(2)*
C(5)	0.8899(5)	-0.0688(5)	0.8705(3)	24(1)*
C(6)	0.7572(5)	-0.1665(5)	0.8194(3)	23(1)*
C(7)	0.6998(5)	-0.3137(5)	0.6492(4)	25(1)*
C(8)	0.5184(5)	-0.5002(5)	0.6734(3)	26(1)*
C(9)	0.4826(6)	-0.5615(6)	0.7794(4)	33(2)*
C(10)	0.3797(6)	-0.4313(7)	0.6020(4)	37(2)*
C(11)	0.5872(6)	-0.6152(6)	0.6111(4)	37(2)*
C(12)	0.8932(5)	-0.0245(5)	0.9890(3)	22(1)*
C(13)	0.9733(6)	-0.1089(6)	1.0756(4)	36(2)*
C(14)	0.9804(6)	-0.0724(7)	1.1852(4)	36(2)*
C(15)	0.9081(5)	0.0503(6)	1.2104(4)	32(1)*
C(16)	0.8272(5)	0.1337(6)	1.1270(4)	31(1)*
C(17)	0.8177(5)	0.0960(5)	1.0157(4)	25(1)*
C(18)	0.6026(5)	-0.0983(5)	0.8166(3)	27(1)*
C(19)	0.5340(5)	-0.1088(6)	0.9092(3)	30(1)*
C(20)	0.3964(6)	-0.0397(6)	0.9105(4)	36(2)*
C(21)	0.3271(5)	0.0389(6)	0.8193(4)	36(2)*
C(22)	0.3918(6)	0.0478(6)	0.7252(4)	34(2)*
C(23)	0.5283(5)	-0.0200(5)	0.7258(3)	27(1)*
O(1)	0.8850(3)	0.0587(4)	0.8031(2)	27(1)*
O(2)	0.9032(4)	0.1356(4)	0.6368(3)	35(1)*
O(3)	0.6891(4)	-0.3355(4)	0.5496(2)	30(1)*
O(4)	0.6314(4)	-0.3900(4)	0.7174(2)	26(1)*
N(1)	0.7816(4)	-0.2042(4)	0.7077(3)	25(1)*

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

Table 2. Bond lengths (Å) for **126b**.

C(1)-C(4)	1.496(7)	C(1)-C(2)	1.338(7)
C(1)-N(1)	1.428(6)	C(4)-O(1)	1.357(5)
C(4)-O(2)	1.197(6)	C(2)-H(2)	0.960(1)
C(2)-C(3)	1.499(7)	C(3)-H(3A)	0.960(1)
C(3)-H(3B)	0.960(1)	C(3)-H(3C)	0.960(1)
C(5)-H(5)	0.960(1)	C(5)-C(6)	1.532(6)
C(5)-C(12)	1.503(6)	C(5)-O(1)	1.451(6)
C(6)-H(6)	0.960(1)	C(6)-C(18)	1.520(7)
C(6)-N(1)	1.471(5)	C(7)-O(3)	1.220(5)
C(7)-O(4)	1.339(6)	C(7)-N(1)	1.378(6)
C(8)-C(9)	1.511(7)	C(8)-C(10)	1.513(6)
C(8)-C(11)	1.523(8)	C(8)-O(4)	1.472(5)
C(9)-H(9A)	0.960(1)	C(9)-H(9B)	0.960(1)
C(9)-H(9C)	0.960(1)	C(10)-H(10A)	0.960(1)
C(10)-H(10B)	0.960(1)	C(10)-H(10C)	0.960(1)
C(11)-H(11A)	0.960(1)	C(11)-H(11B)	0.960(1)
C(11)-H(11C)	0.960(1)	C(12)-C(13)	1.401(6)
C(12)-C(17)	1.392(7)	C(13)-H(13)	0.960(1)
C(13)-C(14)	1.373(6)	C(14)-H(14)	0.960(1)
C(14)-C(15)	1.388(8)	C(15)-H(15)	0.960(1)
C(15)-C(16)	1.373(7)	C(16)-H(16)	0.960(1)
C(16)-C(17)	1.393(6)	C(17)-H(17)	0.960(1)
C(18)-C(19)	1.397(7)	C(18)-C(23)	1.387(6)
C(19)-H(19)	0.960(1)	C(19)-C(20)	1.396(7)
C(20)-H(20)	0.960(1)	C(20)-C(21)	1.377(7)
C(21)-H(21)	0.960(1)	C(21)-C(22)	1.393(7)
C(22)-H(22)	0.960(1)	C(22)-C(23)	1.377(7)
C(23)-H(23)	0.960(1)		

Table 3. Bond angles (deg) for **126b**.

C(4)-C(1)-C(2)	121.5(4)	C(4)-C(1)-N(1)	115.3(4)
C(2)-C(1)-N(1)	123.2(4)	C(1)-C(4)-O(1)	116.1(4)
C(1)-C(4)-O(2)	125.3(4)	O(1)-C(4)-O(2)	118.6(4)
C(1)-C(2)-H(2)	116.3(3)	C(1)-C(2)-C(3)	127.3(5)
H(2)-C(2)-C(3)	116.3(3)	C(2)-C(3)-H(3A)	108.7(3)
C(2)-C(3)-H(3B)	108.1(3)	H(3A)-C(3)-H(3B)	109.5(1)
C(2)-C(3)-H(3C)	111.6(2)	H(3A)-C(3)-H(3C)	109.5(1)
H(3B)-C(3)-H(3C)	109.5(1)	H(5)-C(5)-C(6)	105.3(3)
H(5)-C(5)-C(12)	106.5(2)	C(6)-C(5)-C(12)	115.0(4)
H(5)-C(5)-O(1)	112.5(2)	C(6)-C(5)-O(1)	109.4(3)
C(12)-C(5)-O(1)	108.2(4)	C(5)-C(6)-H(6)	110.9(2)
C(5)-C(6)-C(18)	112.6(4)	H(6)-C(6)-C(18)	103.9(2)
C(5)-C(6)-N(1)	106.0(4)	H(6)-C(6)-N(1)	110.8(2)
C(18)-C(6)-N(1)	112.7(3)	O(3)-C(7)-O(4)	125.4(4)
O(3)-C(7)-N(1)	124.8(5)	O(4)-C(7)-N(1)	109.8(4)
C(9)-C(8)-C(10)	111.5(4)	C(9)-C(8)-C(11)	109.6(4)
C(10)-C(8)-C(11)	112.5(4)	C(9)-C98)-O(4)	101.8(3)
C(10)-C(8)-O(4)	109.5(4)	C(11)-C(8)-O(4)	111.4(4)
C(8)-C(9)-H(9A)	106.3(2)	C(8)-C(9)-H(9B)	118.8(3)
H(9A)-C(9)-H(9B)	109.5(1)	C(8)-C(9)-H(9C)	102.9(3)
H(9A)-C(9)-H(9C)	109.5(1)	H(9B)-C(9)-H(9C)	109.5(1)
C(8)-C(10)-H(10A)	110.1(3)	C(8)-C(10)-H(10B)	101.4(3)
H(10A)-C(10)-H(10B)	109.5(1)	C(8)-C(10)-H(10C)	116.6(3)
H(10A)-C(10)-H(10C)	109.5(1)	H(10B)-C(10)-H(10C)	109.5(1)
C(8)-C(11)-H(11A)	108.7(3)	C(8)-C(11)-H(11B)	115.4(2)
H(11A)-C(11)-H(11B)	109.5(1)	C(8)-C(11)-H(11C)	104.1(3)
H(11A)-C(11)-H(11C)	109.5(1)	H(11B)-C(11)-H(11C)	109.5(1)
C(5)-C(12)-C(13)	118.7(4)	C(5)-C(12)-C(17)	122.4(4)
C(13)-C(12)-C(17)	118.8(4)	C(12)-C(13)-H(13)	119.5(3)
C(12)-C(13)-C(14)	120.9(5)	H(13)-C(13)-C(14)	119.5(3)
C(13)-C(14)-H(14)	120.2(3)	C(13)-C(14)-C(15)	119.5(5)
H(14)-C(14)-C(15)	120.2(2)	C(14)-C(15)-H(15)	119.7(2)
C(14)-C(15)-C(16)	120.7(4)	H(15)-C(15)-C(16)	119.7(3)
C(15)-C(16)-H(16)	120.0(3)	C(15)-C(16)-C(17)	120.0(5)
H(16)-C(16)-C(17)	120.0(3)	C(12)-C(17)-C(16)	120.0(4)
C(12)-C(17)-H(17)	120.2(2)	C(16)-C(17)-H(17)	120.0(3)
C(6)-C(18)-C(19)	120.2(4)	C(6)-C(18)-C(23)	122.0(4)
C(19)-C(18)-C(23)	117.9(4)	C(18)-C(19)-H(19)	119.7(3)
C(18)-C(19)-C(20)	120.6(4)	H(19)-C(19)-C(20)	119.7(3)
C(19)-C(20)-H(20)	120.1(3)	C(19)-C(20)-C(21)	119.8(5)
H(20)-C(20)-C(21)	120.1(3)	C(20)-C(21)-H(21)	119.8(3)
C(20)-C(21)-C(22)	120.4(5)	H(21)-C(21)-C(22)	119.8(3)
C(21)-C(22)-H(22)	120.5(3)	C(21)-C(22)-C(23)	119.0(4)
H(22)-C(22)-C(23)	120.5(3)	C(18)-C(23)-C(22)	122.2(5)
C(18)-C(23)-H(23)	118.9(3)	C(22)-C(23)-H(23)	118.9(3)
C(4)-O(1)-C(5)	114.9(4)	C(7)-O(4)-C(8)	121.1(3)
C(1)-N(1)-C(6)	118.8(4)	C(1)-N(1)-C(7)	120.9(4)
C(6)-N(1)-C(7)	120.0(4)		

Table 4. Anistropic thermal parameters ($Å^2$ x 10^3) for **126b**.

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	27(2)	27(2)	17(2)	6(2)	1(2)	-2(2)
C(4)	27(2)	30(3)	23(2)	2(2)	2(2)	-0(2)
C(2)	33(3)	23(2)	25(2)	3(2)	4(2)	2(2)
C(3)	41(3)	34(3)	29(2)	-2(2)	13(2)	-7(2)
C(5)	31(2)	20(2)	21(2)	1(2)	3(2)	0(2)
C(6)	34(2)	20(2)	16(2)	-0(2)	3(2)	-4(2)
C(7)	26(2)	25(2)	27(2)	-1(2)	9(2)	1(2)
C(8)	28(2)	25(2)	25(2)	-5(2)	5(2)	-5(2)
C(9)	37(3)	30(3)	33(2)	-2(2)	9(2)	-3(2)
C(10)	31(2)	50(3)	28(2)	6(2)	5(2)	-1(3)
C(11)	36(3)	35(3)	44(3)	-12(2)	15(2)	-9(3)
C(12)	22(2)	25(2)	18(2)	-4(2)	1(2)	-5(2)
C(13)	42(3)	33(3)	29(2)	-8(2)	0(2)	9(3)
C(14)	38(3)	44(3)	23(2)	-2(2)	-1(2)	9(3)
C(15)	35(2)	39(3)	22(2)	-6(2)	5(2)	-5(2)
C(16)	33(2)	26(3)	36(2)	-6(2)	12(2)	-0(2)
C(17)	28(2)	21(2)	26(2)	-2(2)	5(2)	-2(2)
C(18)	33(2)	21(2)	24(2)	-5(2)	1(2)	-9(2)
C(19)	35(2)	33(3)	20(2)	-5(2)	4(2)	-10(2)
C(20)	37(3)	47(3)	25(2)	-8(2)	10(2)	-16(3)
C(21)	21(2)	44(3)	40(3)	-9(2)	2(2)	-5(2)
C(22)	35(3)	30(3)	35(2)	-1(2)	0(2)	-3(2)
C(23)	34(3)	22(2)	22(2)	-3(2)	-0(2)	-5(2)
O(1)	31(2)	26(2)	23(1)	-1(1)	2(1)	-3(2)
O(2)	55(2)	24(2)	27(2)	5(1)	11(2)	-5(2)
O(3)	38(2)	33(2)	19(1)	-8(1)	7(1)	-6(2)
O(4)	33(2)	22(2)	22(1)	-5(1)	4(1)	-5(1)
N(1)	31(2)	22(2)	21(2)	-5(2)	7(2)	-2(2)

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

Table 5. Hydrogen atom coordinates (x 10^4) and isotropic thermal parameters (Å x 10^3) for **126b**.

atom	x	y	z	U
H(2)	9460	-2642	5646	33
H(3A)	11567	-1315	5332	47
H(3B)	10780	96	5600	47
H(3C)	10184	-698	4470	47
H(5)	9803	-1240	8716	30
H(6)	7557	-2501	8642	28
H(9A)	3999	-6269	7566	43
H(9B)	4582	-4976	8344	43
H(9C)	5735	-6133	8105	43
H(10A)	3060	-5025	5719	48
H(10B)	4224	-3911	5430	48
H(10C)	3310	-3577	6366	48
H(11A)	5132	-6893	5903	46
H(11B)	6809	-6557	6508	46
H(11C)	6048	-5681	5453	46
H(13)	10239	-1933	10582	42
H(14)	10349	-1314	12439	43
H(15)	9149	771	12869	40
H(16)	7770	2181	11454	39
H(17)	7592	1532	9575	31
H(19)	5820	-1640	9726	36
H(20)	3504	-469	9746	42
H(21)	2334	880	8207	46
H(22)	3421	1004	6609	39
H(23)	5734	-128	6612	35

Compound 126f: See ORTEP drawing on page 210.

Table 1. Atomic coordinates (x 10^4) and isotropic thermal parameters ($Å^2$ x 10^3)[a] for **126f**.

atom	x	y	z	Uiso[b]
N1	3829(3)	2153(2)	2522(1)	24(1)*
O1	6597(2)	147(2)	1580(1)	29(1)*
O2	8769(2)	866(2)	2097(1)	40(1)*
O3	3201(3)	3729(2)	3535(1)	34(1)*
O4	1140(2)	2362(2)	3336(1)	26(1)*
C1	3353(3)	865(2)	2230(1)	22(1)*
C2	4614(3)	549(3)	1453(1)	25(1)*
C3	7139(3)	1134(3)	1964(1)	29(1)*
C4	5616(3)	2477(3)	2213(1)	24(1)*
C5	5884(3)	3843(3)	2176(1)	27(1)*
C6	7619(3)	4384(3)	1935(1)	27(1)*
C7	7658(4)	5698(3)	2251(2)	38(1)*
C8	9212(4)	6301(4)	2097(2)	53(1)*
C9	10770(4)	5623(4)	1617(2)	57(1)*
C10	10777(4)	4349(4)	1264(2)	62(1)*
C11	9188(4)	3728(3)	1414(2)	45(1)*
C12	2750(3)	2845(3)	3176(1)	24(1)*
C13	-97(4)	2651(3)	4085(1)	28(1)*
C14	-1588(4)	1806(3)	4023(2)	42(1)*
C15	1073(4)	2023(3)	4717(2)	41(1)*
C16	-1005(4)	4280(3)	4165(2)	41(1)*
C17	3590(3)	-444(3)	2788(1)	23(1)*
C18	2452(3)	-1439(3)	2787(1)	26(1)*
C19	2632(4)	-2636(3)	3286(2)	33(1)*
C20	3928(4)	-2857(3)	3803(2)	35(1)*
C21	5052(4)	-1871(3)	3815(2)	37(1)*
C22	4887(4)	-672(3)	3312(1)	28(1)*
C23	4253(4)	-656(3)	1008(1)	28(1)*
C24	5604(4)	-1969(3)	861(2)	39(1)*
C25	5233(5)	-3027(3)	429(2)	48(1)*
C26	3541(5)	-2783(3)	138(2)	49(1)*
C27	2178(5)	-1487(3)	287(2)	48(1)*
C28	2537(4)	-422(3)	720(2)	38(1)*

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

(b) For values with asterisks, the equivalent isotropic U is defined as 1/3 of the trace of the U_{ij} tensor.

Table 2. Bond lengths (Å)[a] for **126f**.

N1-C1	1.474(3)	N1-C4	1.429(3)
N1-C12	1.389(3)	O1-C2	1.447(3)
O1-C3	1.343(3)	O2-C3	1.207(3)
O3-C12	1.205(3)	O4-C12	1.344(3)
O4-C13	1.482(3)	C1-C2	1.530(3)
C1-C17	1.523(3)	C2-C23	1.507(4)
C3-C4	1.493(3)	C4-C5	1.339(4)
C5-C6	1.470(4)	C6-C7	1.389(4)
C6-C11	1.387(3)	C7-C8	1.370(5)
C8-C9	1.349(4)	C9-C10	1.376(5)
C10-C11	1.403(5)	C13-C14	1.511(4)
C13-C15	1.511(4)	C13-C16	1.512(3)
C17-C18	1.392(4)	C17-C22	1.392(4)
C18-C19	1.379(3)	C19-C20	1.382(4)
C20-C21	1.380(4)	C21-C22	1.385(4)
C23-C24	1.382(3)	C23-C28	1.382(4)
C24-C25	1.384(5)	C25-C26	1.368(5)
C26-C27	1.374(4)	C27-C28	1.387(5)

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

Table 3. Bond angles (deg)[a] for **126f**.

C1-N1-C4	118.1(2)	C1-N1-C12	120.1(2)
C4-N1-C12	120.7(2)	C2-O1-C3	115.1(2)
C12-O4-C13	121.0(2)	N1-C1-C2	105.5(2)
N1-C1-C17	112.8(2)	C2-C1-C17	113.8(2)
O1-C2-C1	108.3(2)	O1-C2-C23	108.3(2)
C1-C2-C23	115.2(2)	O1-C3-O2	118.7(2)
O1-C3-C4	116.0(2)	O2-C3-C4	125.3(3)
N1-C4-C3	112.9(2)	N1-C4-C5	122.7(2)
C3-C4-C5	124.4(2)	C4-C5-C6	130.9(2)
C5-C6-C7	116.2(2)	C5-C6-C11	126.4(3)
C7-C6-C11	117.4(3)	C6-C7-C8	122.3(2)
C7-C8-C9	120.1(3)	C8-C9-C10	120.0(3)
C9-C10-C11	120.4(3)	C6-C11-C10	119.8(3)
N1-C12-O3	125.1(2)	N1-C12-O4	108.5(2)
O3-C12-O4	126.3(2)	O4-C13-C14	101.7(2)
O4-C13-C15	109.1(2)	C14-C13-C15	111.4(2)
O4-C13-C16	110.2(2)	C14-C13-C16	110.9(2)
C15-C13-C16	112.9(2)	C1-C17-C18	119.3(2)
C1-C17-C22	122.3(2)	C18-C17-C22	118.4(2)
C17-C18-C19	120.7(2)	C18-C19-C20	120.6(3)
C19-C20-C21	119.3(2)	C20-C21-C22	120.4(3)
C17-C22-C21	120.7(3)	C2-C23-C24	122.1(2)
C2-C23-C28	118.8(2)	C24-C23-C28	119.0(3)
C23-C24-C25	120.1(3)	C24-C25-C26	120.7(3)
C25-C26-C27	119.8(3)	C26-C27-C28	119.9(3)
C23-C28-C27	120.5(2)		

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

Table 4. Anisotropic thermal parameters ($Å^2 \times 10^3$)[a,b] for **126f**.

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	19(1)	25(1)	29(1)	-3(1)	-1(1)	-10(1)
O1	19(1)	30(1)	37(1)	-5(1)	1(1)	-4(1)
O2	20(1)	38(1)	63(1)	3(1)	-9(1)	-6(1)
O3	38(1)	33(1)	36(1)	-9(1)	-1(1)	-19(1)
O4	22(1)	31(1)	27(1)	-6(1)	2(1)	-10(1)
C1	17(1)	22(1)	29(1)	-4(1)	-3(1)	-7(1)
C2	20(1)	26(1)	27(1)	1(1)	-3(1)	-4(1)
C3	21(1)	31(1)	34(1)	5(1)	-2(1)	-9(1)
C4	21(1)	28(1)	25(1)	4(1)	-8(1)	-9(1)
C5	20(1)	30(1)	31(1)	-1(1)	-4(1)	-7(1)
C6	22(1)	31(1)	27(1)	8(1)	-6(1)	-8(1)
C7	37(2)	44(2)	39(2)	2(1)	-1(1)	-23(1)
C8	52(2)	66(2)	55(2)	9(2)	-12(2)	-40(2)
C9	35(2)	66(2)	79(2)	33(2)	-19(2)	-27(2)
C10	27(2)	66(2)	72(2)	30(2)	20(2)	6(2)
C11	40(2)	37(2)	49(2)	9(1)	14(1)	-6(1)
C12	23(1)	23(1)	27(1)	2(1)	-5(1)	-7(1)
C13	27(1)	32(1)	25(1)	-2(1)	3(1)	-9(1)
C14	34(2)	56(2)	37(2)	-10(1)	9(1)	-18(1)
C15	42(2)	47(2)	30(1)	4(1)	-2(1)	-8(1)
C16	40(2)	38(2)	39(2)	-4(1)	4(1)	-0(1)
C17	22(1)	25(1)	20(1)	-6(1)	2(1)	-3(1)
C18	23(1)	27(1)	29(1)	-4(1)	0(1)	-8(1)
C19	33(1)	27(1)	38(2)	-2(1)	3(1)	-9(1)
C20	39(2)	31(1)	31(1)	10(1)	0(1)	-5(1)
C21	37(2)	40(2)	31(1)	-1(1)	-9(1)	-4(1)
C22	29(1)	28(1)	28(1)	-4(1)	-3(1)	-8(1)
C23	34(1)	29(1)	20(1)	-1(1)	3(1)	-10(1)
C24	45(2)	33(2)	34(2)	-3(1)	1(1)	-5(1)
C25	68(2)	33(2)	37(2)	-7(1)	9(1)	-10(1)
C26	84(2)	38(2)	28(2)	-5(1)	0(1)	-28(2)
C27	64(2)	47(2)	39(2)	-5(1)	-16(1)	-22(2)
C28	46(2)	35(2)	34(1)	-9(1)	-9(1)	-9(1)

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

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

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

Table 5. Hydrogen coordinates (x 10^4) and thermal parameters ($Å^2$ x 10^3) for **126f**.

atom	x	y	z	U_{iso}
H1	2021	1065	2174	25
H2	4300	1429	1146	31
H5	4752	4597	2335	32
H7	6557	6201	2590	46
H8	9193	7205	2331	63
H9	11873	6031	1521	60
H10	11877	3883	914	67
H11	9186	2852	1157	53
H14A	-2474	1904	4489	49
H14B	-965	786	3944	49
H14C	-2267	2186	3601	49
H15A	232	2084	5195	48
H15B	2007	2578	4744	48
H15C	1712	1011	4618	48
H16A	-1916	4403	4625	49
H16B	-1659	4617	3732	49
H16C	-81	4843	4196	49
H18	1532	-1291	2436	32
H19	1851	-3321	3273	40
H20	4045	-3688	4151	43
H21	5954	-2017	4173	43
H22	5675	8	3326	34
H24	6802	-2148	1058	47
H25	6173	-3940	332	57
H26	3306	-3515	-169	56
H27	980	-1320	92	56
H28	1585	484	821	46

Compound 126a: See ORTEP drawing on page 211.

Table 1. Atomic coordinates (x 10^4) and isotropic thermal parameters ($Å^2$ x 10^3)[a] for **126a**.

atom	x	y	z	U_{iso}[b]
N1	3347(5)	-761(4)	1482(3)	20(2)*
O1	1755(4)	1163(4)	1012(3)	27(1)*
O2	2634(4)	1255(4)	-203(3)	40(2)*
O3	4906(4)	-2166(4)	1280(3)	28(1)*
O4	4171(4)	-1717(4)	2555(3)	26(1)*
C1	3246(6)	-440(6)	635(4)	25(2)*
C2	2543(5)	705(7)	430(4)	28(2)*
C3	1479(5)	354(6)	1702(4)	22(2)*
C4	2681(5)	-56(5)	2100(4)	20(2)*
C5	3668(6)	-1052(7)	-10(4)	36(2)*
C6	4229(6)	-1616(5)	1736(4)	24(2)*
C7	5135(6)	-2412(6)	3023(4)	24(2)*
C8	5125(7)	-3736(6)	2785(5)	40(2)*
C9	4686(6)	-2236(6)	3902(4)	30(2)*
C10	6344(6)	-1743(8)	2890(4)	41(3)*
C11	3463(5)	973(5)	2462(4)	21(2)*
C12	3363(6)	1240(6)	3298(4)	31(2)*
C13	4068(7)	2142(6)	3655(4)	36(2)*
C14	4895(7)	2794(6)	3192(5)	42(3)*
C15	5033(7)	2540(6)	2368(5)	41(3)*
C16	4315(6)	1634(6)	2000(4)	32(2)*
C17	547(5)	1003(5)	2217(4)	19(2)*
C18	-589(6)	473(6)	2340(4)	30(2)*
C19	-1514(6)	1070(7)	2762(5)	42(3)*
C20	-1314(6)	2235(6)	3081(4)	33(2)*
C21	-177(6)	2779(6)	2980(4)	33(2)*
C22	747(6)	2174(6)	2544(4)	25(2)*

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

(b) For values with asterisks, the equivalent isotropic U is defined as 1/3 of the trace of the U_{ij} tensor.

Table 2. Bond lengths for **126a**.

N1-C1	1.424(8)	N1-C4	1.456(8)
N1-C6	1.396(8)	O1-C2	1.369(8)
O1-C3	1.456(7)	O2-C2	1.194(8)
O3-C6	1.204(8)	O4-C6	1.336(8)
O4-C7	1.499(7)	C1-C2	1.497(9)
C1-C5	1.322(10)	C3-C4	1.523(8)
C3-C17	1.491(8)	C4-C11	1.523(8)
C7-C8	1.490(9)	C7-C9	1.520(9)
C7-C10	1.516(9)	C11-C12	1.393(9)
C11-C16	1.391(9)	C12-C13	1.372(10)
C13-C14	1.369(11)	C14-C15	1.375(11)
C15-C16	1.391(10)	C17-C18	1.376(8)
C17-C22	1.396(8)	C18-C19	1.378(10)
C19-C20	1.385(10)	C20-C21	1.379(10)
C21-C22	1.393(9)		

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

Table 3. Bond angles (deg)[a] for **126a**.

C1-N1-C4	119.9(5)	C1-N1-C6	120.2(5)
C4-N1-C6	119.1(5)	O2-O1-C3	116.2(5)
C6-O4-C7	121.0(5)	N1-C1-C2	117.2(5)
N1-C1-C5	128.0(6)	C2-C1-C5	114.7(6)
O1-C2-O2	117.7(6)	O1-C2-C1	117.9(6)
O2-C2-C1	124.4(6)	O1-C3-C4	109.1(5)
O1-C3-C17	106.7(5)	C4-C3-C17	118.9(5)
N1-C4-C3	106.7(5)	N1-C4-C11	112.1(5)
C3-C4-C11	115.3(5)	N1-C6-O3	124.5(6)
N1-C6-O4	108.5(5)	O3-C6-O4	127.0(6)
O4-C7-C8	110.4(5)	O4-C7-C9	101.0(5)
C8-C7-C9	111.3(6)	O4-C7-C10	106.9(5)
C8-C7-C10	115.6(6)	C9-C7-C10	110.6(5)
C4-C11-C12	119.1(5)	C4-C11-C16	122.8(6)
C12-C11-C16	118.1(6)	C11-C12-C13	121.1(5)
C12-C13-C14	120.2(7)	C13-C14-C15	120.2(7)
C14-C15-C16	119.9(7)	C11-C16-C15	120.4(7)
C3-C17-C18	119.5(5)	C3-C17-C22	122.6(5)
C18-C17-C22	117.7(6)	C17-C18-C19	122.0(6)
C18-C19-C20	120.1(6)	C19-C20-C21	119.2(6)
C20-C21-C22	120.3(6)	C17-C22-C21	120.7(6)

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

Table 4. Anisotropic thermal parameters ($Å^2 \times 10^3$)[a,b] for **126a**.

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	28(3)	20(3)	11(2)	1(2)	-1(2)	-2(2)
O1	34(3)	31(2)	16(2)	8(2)	4(2)	4(2)
O2	42(3)	49(3)	29(3)	15(2)	10(2)	16(2)
O3	25(2)	31(3)	29(2)	-6(2)	-2(2)	9(2)
O4	24(2)	34(2)	20(2)	11(2)	-1(2)	9(2)
C1	20(3)	34(4)	22(3)	9(3)	4(3)	-4(3)
C2	17(3)	47(4)	21(4)	5(3)	-2(3)	0(3)
C3	17(3)	24(3)	24(3)	11(3)	-1(3)	-6(3)
C4	22(3)	18(3)	21(3)	11(3)	8(3)	-0(3)
C5	45(4)	40(4)	23(4)	-0(3)	6(3)	9(3)
C6	25(3)	15(3)	32(4)	-8(3)	-9(3)	2(3)
C7	17(3)	33(4)	20(3)	5(3)	-6(3)	4(3)
C8	44(4)	33(4)	42(5)	5(4)	-19(4)	11(4)
C9	29(4)	31(4)	30(4)	3(3)	-4(3)	1(3)
C10	30(4)	57(5)	34(4)	1(4)	8(3)	-7(4)
C11	18(3)	20(3)	25(3)	0(3)	0(3)	6(3)
C12	35(4)	29(4)	29(4)	-6(3)	-1(3)	3(3)
C13	47(4)	34(4)	28(4)	1(3)	-5(3)	6(3)
C14	49(5)	29(4)	48(5)	-11(4)	-21(4)	-3(4)
C15	41(4)	33(4)	48(5)	5(4)	-3(4)	-10(3)
C16	27(4)	38(4)	32(4)	0(3)	3(3)	-14(3)
C17	17(3)	19(3)	21(3)	4(3)	2(3)	3(2)
C18	22(3)	36(4)	33(4)	-5(3)	-2(3)	2(3)
C19	30(4)	46(5)	51(5)	-9(4)	13(4)	-5(3)
C20	33(4)	40(4)	24(4)	2(3)	5(3)	10(3)
C21	37(4)	33(4)	27(4)	-5(3)	-9(3)	3(3)
C22	28(3)	25(3)	23(3)	10(3)	1(3)	-5(3)

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

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

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

Table 5. Hydrogen coordinates (x 10^4) and thermal parameters ($Å^2$ x 10^3) for **126a**.

atom	x	y	z	Uiso
H3	1102	-417	1561	25
H4	2490	-544	2576	27
H5A	3513	-751	-556	37
H5B	4128	-1797	68	37
H8A	5332	-3873	2218	0
H8B	4294	-3999	2883	0
H8C	5674	-4198	3130	0
H9A	5291	-2595	4259	35
H9B	3929	-2686	3947	35
H9C	4550	-1394	4057	35
H10A	6858	-2185	3269	46
H10B	6314	-891	3045	46
H10C	6676	-1815	2345	46
H12	2791	785	3630	33
H13	3981	2316	4231	41
H14	5380	3430	3443	55
H15	5624	2989	2047	54
H16	4409	1463	1424	39
H18	-743	-336	2125	37
H19	-2298	678	2837	56
H20	-1959	2661	3368	41
H21	-21	3576	3213	37
H22	1529	2569	2466	30

Compound 132: See ORTEP drawing on page 212.

Table 1. Atomic coordinates (x 10^5) and equivalent isotropic displacement coefficients (Å x 10^4) for **132**.

atom	x	y	z	U(eq)
Br	3396(7)	4664(4)	29899(3)	373(2)
C1	22212(65)	15661(39)	24517(26)	276(13)
C2	42181(75)	12686(43)	23895(33)	377(16)
C3	55882(71)	20959(42)	20201(29)	332(14)
C4	50273(61)	32217(38)	17438(23)	215(12)
C5	30000(65)	34687(40)	17847(23)	227(12)
C6	15930(65)	26527(38)	21389(24)	243(12)
C7	66350(62)	40644(39)	13751(23)	231(12)
C8	61322(58)	58178(36)	23269(22)	191(11)
C9	72115(60)	71595(38)	24413(23)	216(12)
C10	98947(64)	67945(39)	16408(24)	250(13)
C11	79946(61)	62031(38)	10904(24)	220(12)
C12	80646(71)	59814(45)	2015(25)	308(14)
C13	69876(69)	70204(44)	4564(25)	310(14)
C14	79119(90)	83409(49)	3355(34)	459(18)
C15	71140(141)	92939(61)	7775(43)	713(29)
C16	68035(59)	50558(35)	30459(22)	193(11)
C17	87932(62)	46859(38)	31863(25)	239(12)
C18	93298(73)	40057(44)	38647(28)	320(14)
C19	79225(75)	37125(44)	44164(26)	329(14)
C20	59438(78)	40776(41)	42895(26)	318(14)
C21	53862(64)	47511(38)	36068(25)	239(12)
C22	69537(63)	77220(36)	32587(24)	224(12)
C23	50252(66)	80874(38)	33651(25)	265(13)
C24	47183(70)	85611(40)	41335(27)	285(13)
C25	63231(76)	86672(43)	47755(27)	326(14)
C26	82123(75)	82998(41)	46598(27)	314(14)
C27	85341(69)	78222(39)	39169(24)	261(13)
N1	66730(50)	53205(31)	15332(19)	205(10)
O1	78234(46)	36533(27)	9609(17)	275(9)
O2	94143(42)	72253(26)	23590(17)	231(8)
O3	116793(46)	69106(32)	15018(19)	334(10)

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

Table 2. Bond lengths (Å) for **132**.

Br-C1	1.905(4)	C1-C2	1.393(7)
C1-C6	1.391(6)	C2-C3	1.383(7)
C3-C4	1.394(6)	C4-C5	1.388(6)
C4-C7	1.491(6)	C5-C6	1.378(6)
C7-N1	1.384(5)	C7-O1	1.212(5)
C8-C9	1.532(5)	C8-C16	1.513(5)
C8-N1	1.502(5)	C9-C22	1.504(6)
C9-O2	1.446(5)	C10-C11	1.502(5)
C10-O2	1.349(5)	C10-O3	1.200(5)
C11-C12	1.485(6)	C11-C13	1.528(6)
C11-N1	1.467(5)	C12-C13	1.486(7)
C13-C14	1.510(7)	C14-C15	1.442(10)
C16-C17	1.399(6)	C16-C21	1.395(6)
C17-C18	1.387(6)	C18-C19	1.377(7)
C19-C20	1.389(7)	C20-C21	1.392(6)
C22-C23	1.394(6)	C22-C27	1.391(5)
C23-C24	1.402(6)	C24-C25	1.383(6)
C25-C26	1.374(7)	C26-C27	1.369(6)

Table 3. Bond angles (deg) for **132**.

Br-C1-C2	119.0(3)	Br-C1-C6	119.7(3)
C1-C2-C6	121.3(4)	C1-C2-C3	118.3(4)
C2-C3-C4	121.3(4)	C3-C4-C5	119.0(4)
C3-C4-C7	117.2(4)	C5-C4-C7	123.8(4)
C4-C5-C6	120.8(4)	C1-C6-C5	119.2(4)
C4-C7-N1	116.2(4)	C4-C7-O1	120.9(4)
N1-C7-O1	122.9(4)	C9-C8-C16	111.1(3)
C9-C8-N1	106.8(3)	C16-C8-N1	112.3(3)
C8-C9-C22	111.8(3)	C8-C9-O2	110.6(3)
C22-C9-O2	109.6(3)	C11-C10-O2	112.4(3)
C11-C10-O3	127.4(4)	O2-C10-O3	120.2(3)
C10-C11-C12	121.1(4)	C10-C11-C13	117.1(3)
C12-C11-C13	59.1(3)	C10-C11-N1	111.2(3)
C12-C11-N1	119.6(3)	C13-C11-N1	120.0(3)
C11-C12-C13	61.9(3)	C11-C13-C12	59.0(3)
C11-C13-C14	122.6(4)	C12-C13-C14	119.7(4)
C13-C14-C15	116.5(5)	C8-C16-C17	123.0(4)
C8-C16-C21	118.0(4)	C17-C16-C21	119.0(4)
C16-C17-C18	120.4(4)	C17-C18-C19	120.2(4)
C18-C19-C20	120.2(4)	C19-C20-C21	119.9(4)
C16-C21-C20	120.3(4)	C9-C22-C23	118.3(3)
C9-C22-C27	122.0(4)	C23-C22-C27	119.6(4)
C22-C23-C24	119.3(4)	C23-C24-C25	120.0(4)
C24-C25-C26	119.8(4)	C25-C26-C27	121.0(4)
C22-C27-C26	120.3(4)	C7-N1-C8	122.0(3)
C7-N1-C11	118.8(3)	C8-N1-C11	115.0(3)
C9-O2-C10	116.5(3)		

Table 4. Anisotropic displacement coefficients (Å2 x 104) for 132.

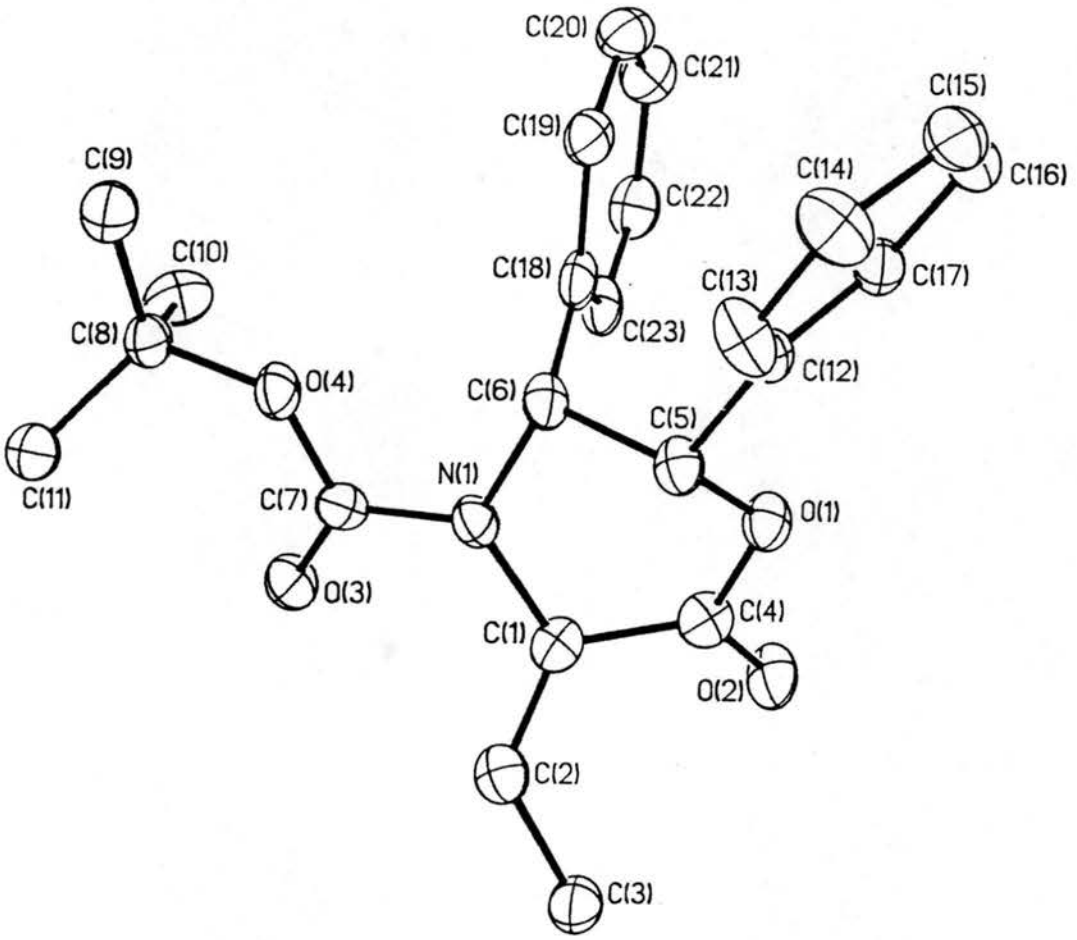
atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br	329(3)	304(3)	463(3)	-57(2)	48(2)	155(2)
C1	245(21)	242(22)	315(22)	-17(17)	-20(17)	27(17)
C2	292(23)	208(22)	640(32)	34(18)	69(21)	126(21)
C3	284(23)	249(23)	471(27)	43(19)	64(20)	67(20)
C4	210(19)	230(21)	206(18)	50(16)	8(15)	-12(16)
C5	255(20)	241(21)	178(18)	33(17)	-4(15)	37(15)
C6	223(19)	218(21)	269(21)	-16(16)	4(15)	10(16)
C7	233(19)	267(21)	182(18)	40(17)	-28(15)	28(16)
C8	167(18)	199(20)	207(19)	26(15)	21(14)	1(15)
C9	206(19)	226(20)	216(19)	45(16)	-2(15)	83(16)
C10	257(22)	276(22)	194(19)	0(17)	-33(16)	68(16)
C11	205(19)	229(20)	214(19)	-28(16)	30(15)	58(16)
C12	308(22)	402(26)	210(20)	-39(20)	72(17)	65(18)
C13	279(22)	384(26)	255(21)	27(19)	1(17)	82(18)
C14	485(29)	412(30)	493(30)	49(24)	80(24)	286(24)
C15	1132(65)	444(37)	577(39)	139(39)	107(39)	122(30)
C16	226(19)	178(19)	177(18)	37(15)	26(15)	-2(15)
C17	232(20)	230(21)	261(20)	15(16)	71(16)	13(16)
C18	292(22)	329(24)	348(23)	106(19)	-14(18)	101(19)
C19	425(26)	330(25)	244(21)	121(21)	-5(18)	122(18)
C20	500(28)	276(23)	205(20)	49(20)	145(18)	76(17)
C21	240(20)	216(20)	269(20)	63(16)	30(16)	19(16)
C22	255(20)	166(19)	251(20)	24(16)	33(16)	41(15)
C23	273(21)	216(21)	285(22)	26(17)	-35(17)	-9(17)
C24	319(22)	227(22)	327(22)	83(18)	69(18)	-6(18)
C25	398(25)	285(23)	302(23)	34(20)	96(19)	-34(19)
C26	394(25)	263(23)	278(21)	60(20)	0(18)	11(18)
C27	286(21)	240(22)	250(20)	48(17)	0(17)	14(17)
N1	217(16)	224(18)	172(16)	-2(14)	51(13)	-28(13)
O1	326(16)	285(16)	245(14)	79(13)	120(12)	25(12)
O2	194(14)	227(15)	257(14)	-34(11)	34(11)	34(11)
O3	187(15)	452(20)	355(17)	7(13)	38(12)	40(14)

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

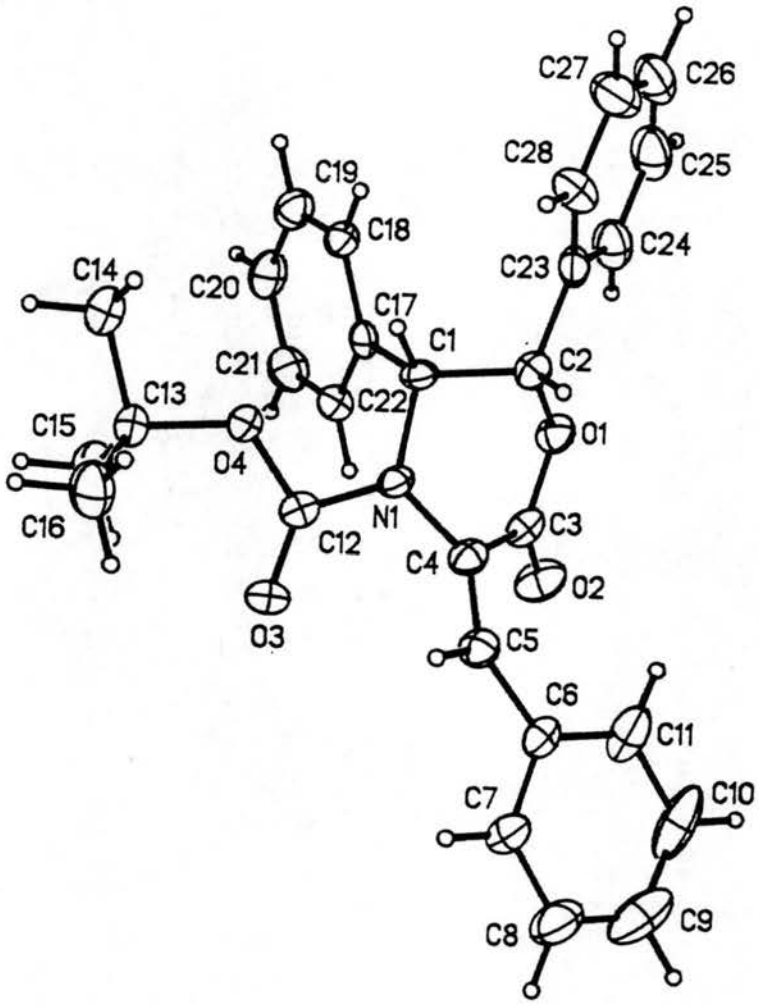
Table 5. H-atom coordinates (x 10^4) and isotropic displacement coefficients ($Å^2$ x 10^3) for **132**.

atom	x	y	z	U
H2	4628	505	2592	47
H3	6955	1893	1958	44
H5	2572	4215	1561	33
H6	198	2833	2171	32
H8	4640	5771	2300	29
H9	6544	7630	2024	30
H12A	9365	6159	-22	41
H12B	7260	5256	-74	41
H13	5617	7265	350	44
H14A	7656	8491	-238	58
H14B	9393	8412	500	58
H15A	7247	10135	606	94
H15B	7819	9265	1323	94
H15C	5660	8979	770	94
H17	9785	4899	2807	34
H18	10694	3749	3954	41
H19	8307	3252	4889	46
H20	4957	3860	4670	41
H21	4023	5010	3524	34
H23	3922	8020	2916	39
H24	3391	8810	4213	44
H25	6111	8993	5301	45
H26	9324	8379	5106	44
H27	9859	7562	3847	39

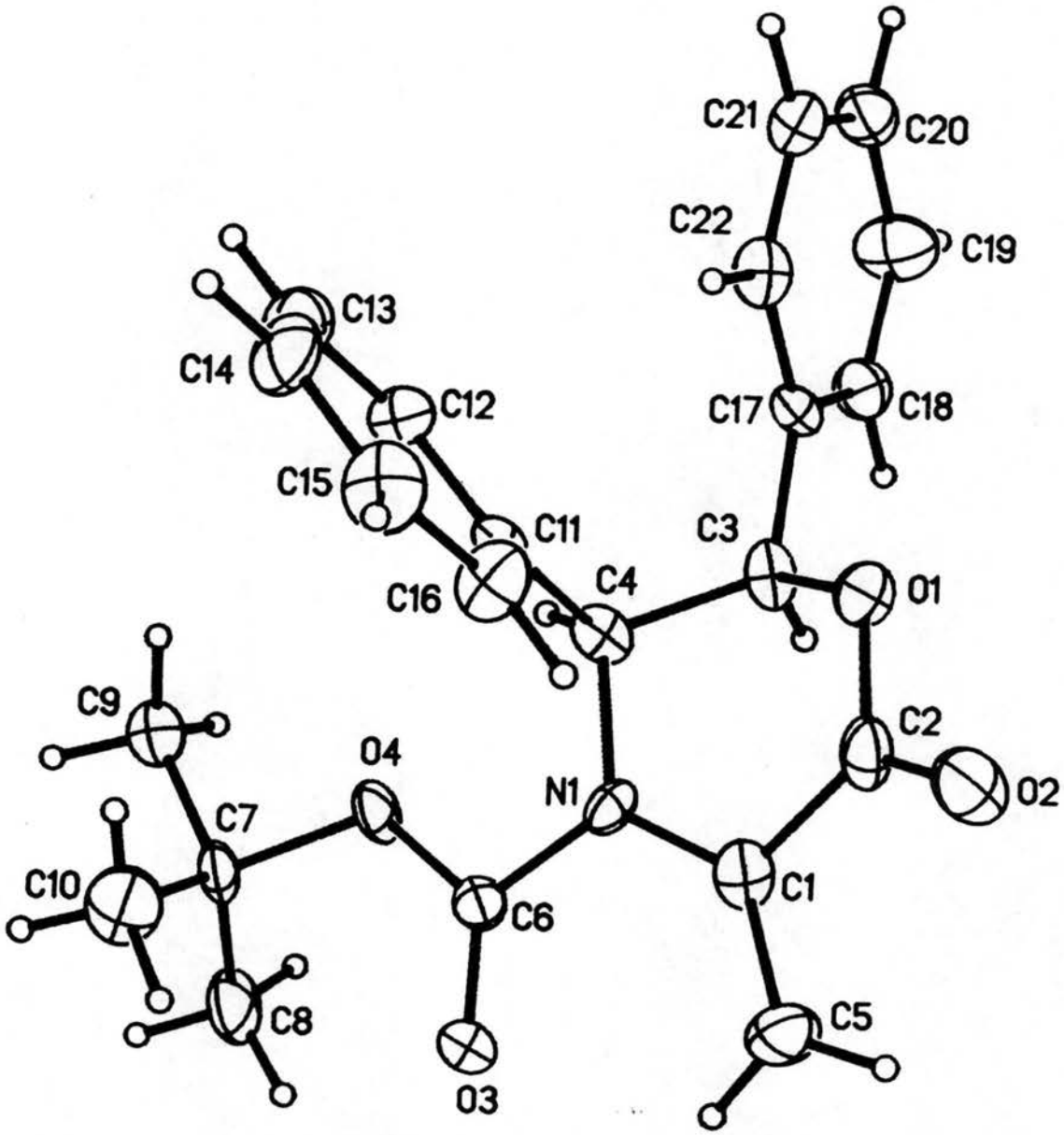
ORTEP drawing for compound **126b**.



ORTEP drawing for compound **126f**.



ORTEP drawing for compound **126a**.



ORTEP drawing for compound **132**.