DISSERTATION

I. TOTAL SYNTHESIS OF BISTRATAMIDE D

II. INVESTIGATIONS OF CHIRAL NON-RACEMIC 5,7-BICYCLIC LACTAMS

Submitted by
Susan V. Downing
Department of Chemistry

In partial fulfillment of the requirements
for the degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Fall 2000

COLORADO STATE UNIVERSITY

July 27, 2000

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY SUSAN V. DOWNING ENTITLED "I. TOTAL SYNTHESIS OF BISTRATAMIDE D II. INVESTIGATIONS OF CHIRAL NON-RACEMIC 5,7-BICYCLIC LACTAMS" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION

I. TOTAL SYNTHESIS OF BISTRATAMIDE D

II. INVESTIGATIONS OF CHIRAL NON-RACEMIC 5,7-BICYCLIC LACTAMS

I. Due to a continued interest shown by the Meyers group in the construction of nitrogen-containing heterocycles, the synthesis of bistratamide D was undertaken. The synthetic strategy involved the convergent assembly of enantiomerically pure oxazole, thiazole, and oxazoline segments, which were derived from amino acid starting materials. Carbodiimide-mediated peptide coupling was utilized to synthesize an oxazole-thiazole tetrapeptide, as well as oxazoline-oxazole-thiazole and oxazole-thiazole-oxazoline hexapeptide sequences. The title compound was prepared in fair yield by macrolactamization of either of these two hexapeptide sequences utilizing *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU).

II. The synthesis and utility of a novel class of compounds, the 5,7-bicyclic lactams, are described. Compounds produced by the cyclodehydration of (*R*)-phenylglycinol with ω-keto acids were obtained as separable diastereomeric mixtures (~2:1 at the angular center) in low yields (~40%). Higher chemical yields (65–87%) were realized through either the use of a keto acid conformationally constrained by a *cis*-alkene (cyclodehydration method), or by the use of a ring closing metathesis strategy to synthesize the bicyclic structure. Neither modification, however, provided improvement in the product diastereoselection.

Stereoselective reductions of the 5,7-bicyclic lactams occurred with the use of alane or lithiumaluminum hydride, affording amino alcohols of the *R* configuration at the 2-position, in good to moderate yields (50–88%). Selectivity was also observed in the

diisobutylaluminum hydride reduction of the *endo* lactam epimers, affording amino alcohols of the opposite configuration at *C*-2. Rationalization for the selectivity in both cases was described to derive from an intramolecular transfer of hydride from the pre-coordinated aluminum reagent to the angular center before complete planarity of the iminium ion was realized. Complexation of the reagent to the less congested face of the bicyclic systems results in "retention" of the relative stereochemistry at this chiral center. Lastly, hydrogenolytic cleavage of the benzyl moiety afforded chiral 2-substituted perhydroazepines in good yields, and good enantiomeric excesses (84–94%).

Susan V. Downing
Department of Chemistry
Colorado State University
Fort Collins, CO 80523
Fall 2000

ACKNOWLEDGMENTS

I am very grateful to have had the opportunity to study under the tutelage of Professor Meyers these last few years. Upon completion of my first project, I inquired about the possibility of exploring a new direction for the lactam chemistry. This *possibility* eventually spun into the project encompassing the majority of this thesis. The support and encouragement he offered me during this time, combined with his hands-off approach to mentoring, has allowed me the occasion to mature as an independent thinker. While it is a shame that future students will not have the fortuity to have Professor Meyers as an advisor, I'd like to extend to him best wishes for a happy, healthful retirement.

It goes without saying that all interactions serve to shape an individual, and that both past and present Meyers group members also had a hand in the development of this work and in my growth as a chemist. Two fantastic people who deserve specific mention are Lori Basil and Mike Dwyer, both of whom entertained countless questions, offered sound chemical advise, and participated in light-hearted chatter with enthusiasm.

Moreover, I am much obliged to the following individuals for helping to make my graduate years more delightful: to all of my field and ice hockey teammates, who play their sports with passion and allowed me to forget about chemistry every once in awhile, to long-time friends Max, Pam, and Steve, who didn't let the miles make us distant, and to Sarah and P, who reminded me I'm loved.

DEDICATION

To my father, for inspiring me to continually challenge myself.

TABLE OF CONTENTS

CHAPTER ONE

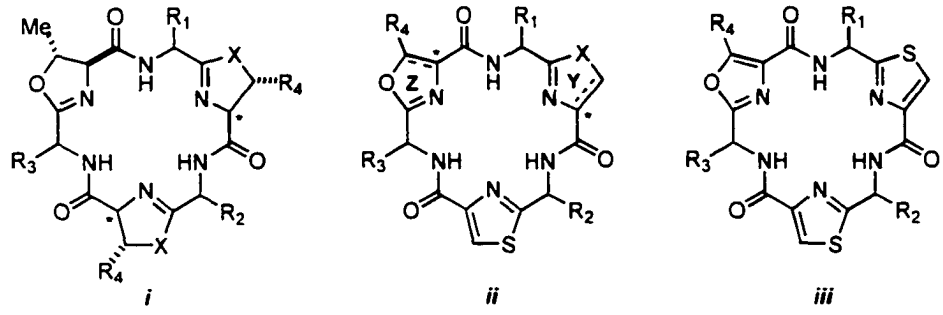
Total Synthesis of Bistratamide D[1]

I. Introduction

A. The Interest in Cyclic Peptide Alkaloids of Marine Origin

A large number of macrocyclic peptide alkaloids have been isolated from marine organisms over the last few decades, in which oxazoline, oxazole, thiazoline, and thiazole heterocycles, derived from modified amino acid residues, are frequently encountered as structural subunits.[2,3] The varied biological activities that these natural products exhibit,[2,3] the possibility of acting as metal ion chelating metabolites,[4] and the presence of high symmetry or pseudosymmetry,[5] have originated a considerable amount of both structural and synthetic studies.[2,3]

One such frequently studied class of cyclic peptides is that isolated from tunicates, or "sea squirts", of the *Lissoclinum* genus. The lissoclinum peptides, as they are known, are 18-24 membered macrocycles characterized by alternating 5-membered ring azole heterocycles and lipophilic amino acid residues. Thus far, about 30 different variants have been isolated, and these have been divided into 3 general classes of substructure, depending on ring size.[2a]



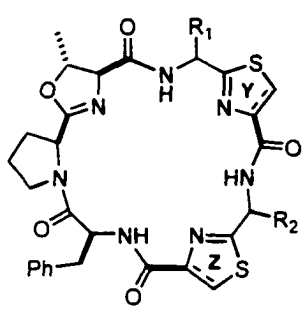
i *ii* *iii*

Table 1.1 Class A Lissoclinum Peptides

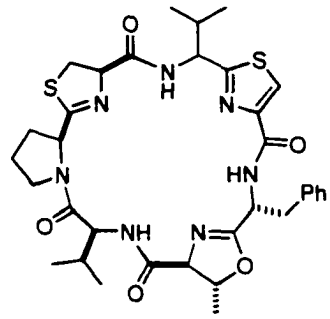
Structure		Name	R_1	R_2	R_3	R_4	X	Y	Y*	Z	Z*
1.1	*i*	Bistratamide A	Me	CH_2Ph	(*S*)-*i*-Pr	H	S		?		
1.2	*ii*	Bistratamide B	Me	CH_2Ph	(*S*)-*i*-Pr	(*R*)-Me	S	TH	?	OX	(*S*)
1.3	*iii*	Bistratamide C	(*S*)-Me	(*S*)-*i*-Pr	(*S*)-*i*-Pr	H					
1.4	*ii*	Bistratamide D	(*S*)-*i*-Pr	(*S*)-*i*-Pr	(*S*)-*i*-Pr	(*R*)-Me	O	OXZ	-	OX	(*S*)
1.5	*i*	Westiellamide	(*S*)-*i*-Pr	(*S*)-*i*-Pr	(*S*)-*i*-Pr	(*R*)-Me	O		(*S*)		
1.6	*ii*	Dolastatin E	(*R*)-Me	(*R*)-	(*S*)-Me	H	S	TH	(*S*)	OXZ	
1.7	*ii*	Dolastatin I	(*S*)-*i*-Pr	(*S*)-Me	(*S*)-	Me	O	OX	(*S*)	OXZ	
1.8	*ii*	Raocyclamide A	(*S*)-Me	(*S*)-	(*R*)-CH_2Ph	H	O	OXZ	-	OX	(*R*)
1.9	*iii*	Nostocyclamide	H	(*R*)-*i*-Pr	(*S*)-Me	Me					
2.0	*iii*	Dendroamide A	(*R*)-*i*-Pr	(*R*)-Me	(*R*)-Me	Me					
2.1	*iii*	Dendroamide B	(*R*)-Me	(*R*)-$(CH_2)_2SCH_3$	(*R*)-Me	Me					
2.2	*iii*	Dendroamide C	(*R*)-Me	(*R*)-$(CH_2)_2SOCH_3$	(*R*)-Me	Me					

TH = thiazoline, OX = oxazoline, OXZ = oxazole

Class A is comprised of the 18-membered macrocycles,[2a] and those known to date are compiled in Table 1.1. Interestingly, fewer than half of these cyclic peptides have been isolated from tunicates. The hexapeptides dolastatin E and I were isolated from the sea hare *Dolabella auricularia*,[3] and raocyclamide A, nostocyclamide, and dendroamides A, B, and C were isolated from the cyanobacteria strains *Oscillatoria raoi*, *Nostoc* sp. 31, and *Stigonema dendrodium*, respectively.[2a] Additionally, the C_3-symmetric cycloxazoline, isolated from *Lissoclinum bistratum*, was independently characterized as westiellamide after isolation from the terrestrial blue-green algae *Westiellopsis prolifica*.[2b] These findings lend credence to the long-held speculation that these secondary metabolites may in fact be produced by the unicellular prokaryotic symbiont *Prochloron*, which is known to reside in both *L. bistratum* and *Dolabella* spp.[2,3]



iv



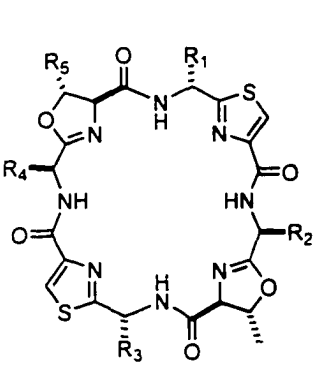
Cyclodidemnamide (**1.22**)

Table 1.2. Class B Lissoclinum Peptides

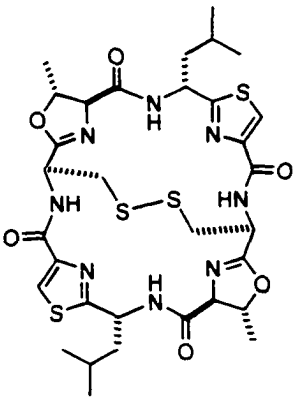
	Name	R_1	R_2	Y	Z
1.13	Lissoclinamide 1	(*S*)-*i*-Pr	(*R*)-	THZ	THZ
1.14	Lissoclinamide 2	(*R*)-	(*R*)-Me	THZ	TH
1.15	Lissoclinamide 3	(*R*)-	(*S*)-Me	THZ	TH
1.16	Lissoclinamide 4	(*S*)-*i*-Pr	(*R*)-CH_2Ph	THZ	TH
1.17	Lissoclinamide 5	(*S*)-*i*-Pr	(*R*)-CH_2Ph	THZ	THZ
1.18	Lissoclinamide 6	(*R*)-*i*-Pr	(*R*)-CH_2Ph	THZ	TH
1.19	Lissoclinamide 7	(*R*)-*i*-Pr	(*R*)-CH_2Ph	TH	TH
1.20	Lissoclinamide 8	*i*-Pr	CH_2Ph	THZ	TH
1.21	Ulicyclamide	(*S*)-	(*R*)-Me	THZ	THZ

THZ = thiazole, TH = thiazoline

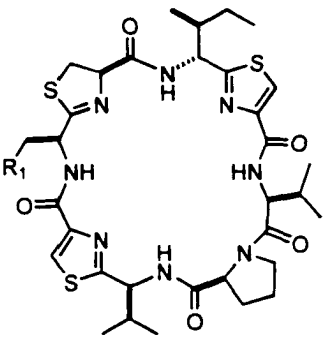
The Class B lissoclinum peptides are shown in Table 1.2 and consist of 21-membered macrocycles, all containing a proline residue. Lissoclinamides 1-8 and ulicyclamide were isolated from various collections of *Lissoclinum patella*.[2a] Configurationally distinct cyclodidemnamide was isolated from the ascidian *Didemnum molle*.[2a] Recent attempts to synthesize this compound have proven that its' assigned structure, incorporating an L-valine thiazole moiety, is incorrect.[2a] The authors surmise that the natural product may instead be derived from D-valine at this center, while others purport that the molecular connectivity may instead exist as in structure ***iv***.[2a] These questions regarding the connectivity and/or stereochemical assignment of a lissoclinum peptide are not new ones, as several have required structural reassignment upon completion of synthetic efforts.[2ab]



v



Ulithiacyclamide (**1.30**)



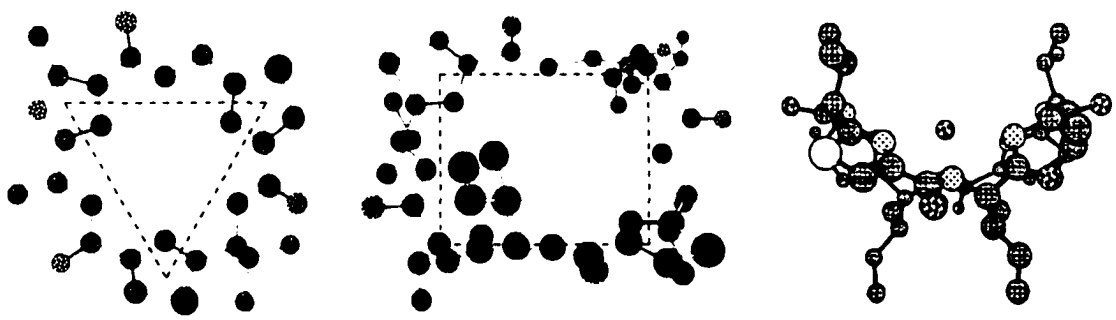
vi

Table 1.3. Class C Lissoclinum Peptides

Structure		Name	R_1	R_2	R_3	R_4	R_5
1.23	*v*	Ascidiacyclamide	*i*-Pr		*i*-Pr		Me
1.24	*v*	Patellamide A	*i*-Pr		*i*-Pr		H
1.25	*v*	Patellamide B	CH_2Ph	*i*-Bu	Me		Me
1.26	*v*	Patellamide C	CH_2Ph	*i*-Pr	Me		Me
1.27	*v*	Patellamide D	Me		CH_2Ph		Me
1.28	*v*	Patellamide E	*i*-Pr		CH_2Ph	*i*-Pr	Me
1.29	*v*	Patellamide F	*i*-Pr	*i*-Pr	CH_2Ph	*i*-Pr	Me
1.30	*vi*	Tawicyclamide A	Ph				
1.31	*vi*	Tawicyclamide B	*i*-Bu				

The last group of lissoclinum peptides, comprising class C, are the 24-membered analogs, each of which has been isolated from *L. patella*.[2a] The potent cytotoxicity of ulithiacyclinamide, containing a unique disulfide bridge, undoubtedly spurred the considerable amount of analytical, biological, and synthetic interest in this class of peptides since it was first described in 1980. Ulithiacyclinamide, together with lissoclinamide 7 (**1.19**), is one of the most cytotoxic of the lissoclinum peptides, with IC_{50} values of 35, 15, and 20 ng/mL in L1210 (mouse leukemia cells), T24 (transitional bladder carcinoma cells), and MRC5CV1 (SV40 transformed fibroblasts) assays, respectively.

Aside from the perhaps unusual appearance that the azole heterocycles impart, these modified amino acid residues affect the chemical, physical and biological properties of their parent molecules as well. While cyclic peptide structures of 18-24 members are considered to maintain considerable backbone flexibility, the 5-membered heterocyclic subunits incorporated into the lissoclinum peptides impart substantial conformational rigidity, such that frequently only one major conformer exists in both the solution and the solid states.[2a] The 18-membered peptides of Class A assume a nearly planar "triangle" conformation in which each nitrogen atom points toward the center of the cavity, each carbonyl oxygen points away from the cavity, and each R group is in an axial position (Figure 1.1).[2a,6a] This conformational preference appears irrespective of the oxidation state of the heterocycles or the size of the pendant R groups.



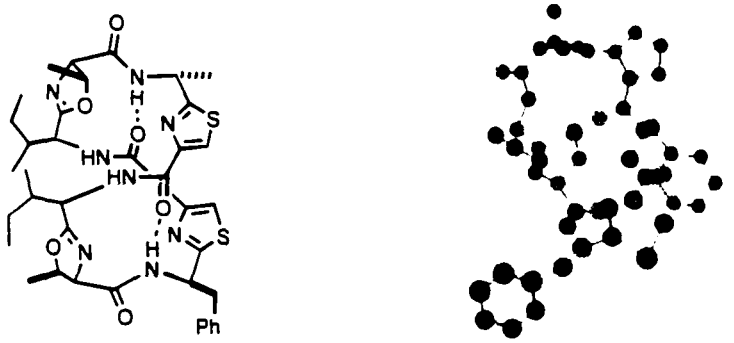
Nostocyclamide (**1.9**) Ascidiacyclamide (**1.23**) Patellamide A (**1.24**)

Figure 1.1. Conformations for class A and C_2-symmetric class C lissoclinum peptides

The conformation of the Class C peptides seems to depend upon the apparent symmetry possessed by the macrocycle. The C_2-symmetric macrocycles adopt a rectangular- or saddle-shape,[2a] depending on whether it is viewed from above, as shown in Figure 1.1 for ascidiacyclamide (**1.23**), or from the side, as shown for patellamide A (**1.24**). In these structures, each of the heterocycles form the corners of a rectangle and, similar to the structure for Class A compounds, each of the N-H bonds

and the azole nitrogen atoms point into the cavity while the carbonyl groups point outward. The pseudo-axial position of the side chains is more easily seen in the side view of patellamide A. Additionally, ulithiacyclamide (**1.30**) has displayed a similar structure in non-polar solvents.

The less symmetrical macrocycle patellamide D (**1.27**) adopts a "twisted 8" conformation, where 4 transannular hydrogen bonds hold the molecule in this folded geometry (Figure 1.2).[2a] In this conformation, the thiazole rings are nearly parallel and only the phenylalanine side chain extends away from the backbone. Patellamide B (**1.25**) and C (**1.26**), and tawicyclamide B (**1.31**), also possess this conformation.



Patellamide D (**1.27**) Lissoclinamide 7 (**1.19**)

Figure 1.2. Conformations for asymmetrical class C and B lissoclinum peptides

Thus far, conformational studies of Class B peptides have been limited to lissoclinamide 7 (**1.19**), for which an essentially similar conformation was observed both in solid and solution phases.[7] In this structure, reproduced in Figure 1.2, the proline and phenylalanine-derived thiazoline heterocycles reside nearly parallel to the plane of the macrocycle, while the oxazoline and valine-derived thiazoline heterocycles are nearly perpendicular. Three hydrogen bonds serve to stabilize a β-turn at the prolyl-oxazoline segment and a β-loop around the thiazoline-phenylalanine-thiazoline moiety.

A potential application of the nearly C_3-symmetric 18-membered lissoclinum peptides is in chiral recognition and asymmetric synthesis.[5] Chiral symmetric hosts and catalysts can offer advantages because several modes of binding with a substrate are equivalent. The reduction of competing alternatives frequently serves to improve the selectivity of such processes.

Lissoclinum peptides have also received attention in regard to their speculated ability to chelate metal ions,[4] and indeed, westiellamide and ascidiacyclamide metal-complexes have been characterized.[2a] Ascidiacyclamide (**1.23**) binds two copper(II) ions, and one carbonate molecule, in the top-side cleft of the saddle conformation shown in Figure 1.1.[8] Each copper atom is chelated by three nitrogen atoms, and the carbonate forms a bridge, held between the two copper atoms, such that the entire complex maintains C_2-symmetry.

Westiellamide (**1.5**) has a high affinity for binding silver, and forms a C_3-symmetric "sandwich" complex comprised of two macrocyclic ligands and four silver(I) ions.[2a] Upon binding, a significant amount of molecular reorganization takes place. Effectively, the macrocycle turns inside out; the central silver atom is chelated by all 6 carbonyl groups, and the isopropyl groups become pseudo-equatorial. The remaining three silver ions are complexed between opposing pairs of oxazoline nitrogen atoms. Evidently, the absence of a pre-organized structure does not preclude binding in this case.

Another consequence of the azole substructure, which is useful in the context of pharmaceutical applications, is that these cyclized forms are less polar than are their open chain serine-, cysteine-, or threonine-containing counterparts which sport pendant hydroxyl or thiol groups. Bioavailability is favorably influenced by both the absence of

ionized termini, which facilitates the crossing of membrane barriers, and an increased resistance to *in vivo* enzymatic degradation.[2b]

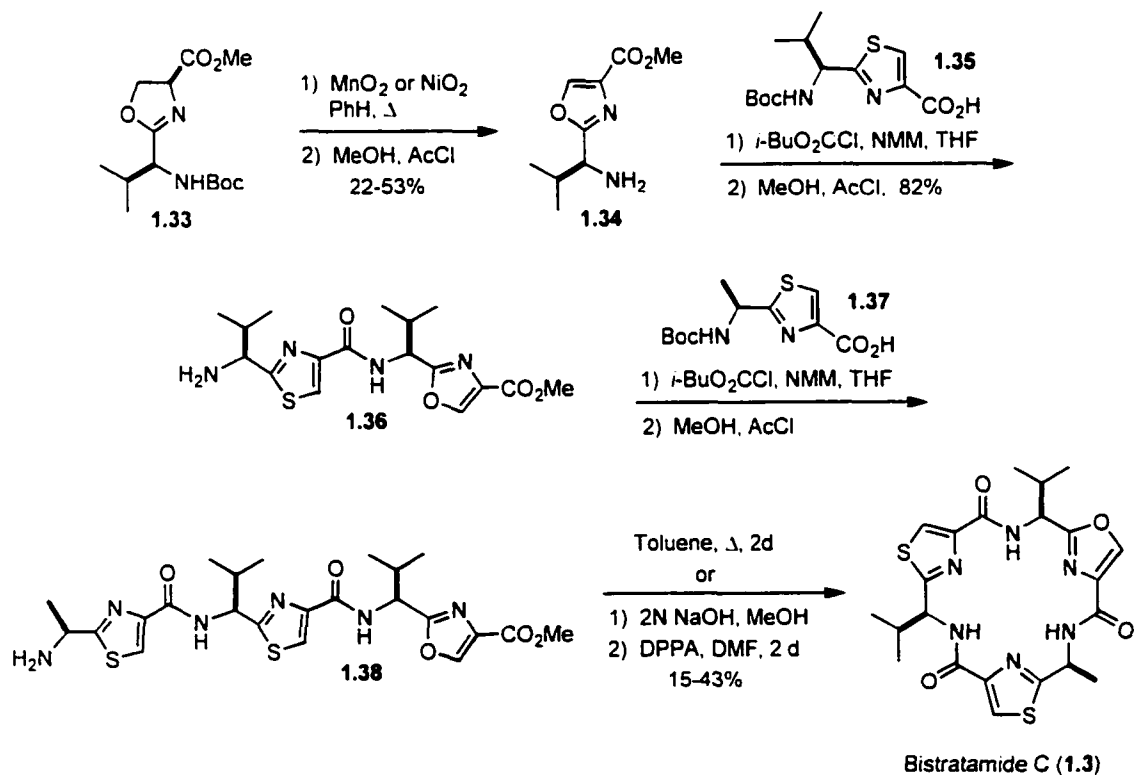
A survey of the literature reveals that most of the lissoclinum peptides display at least moderate cytotoxic activity.[2a] An early structure-activity study of ascidiacyclamide (**1.23**) and patellamide A, B, and C (**1.24-26**) documents the necessity of the oxazoline moiety for the pharmacological properties observed.[9] Even synthetic intermediates containing only half of the peptide residues of the parent compounds exhibited moderate but distinct cytotoxicity as long as this functionality remained intact. More recently, the replacement of the thiazolines of lissoclinamide 7 (**1.19**) with oxazolines has been shown to cause a significant decrease in cytotoxic properties, while exchange of the one oxazoline for a thiazoline lead to attenuation of the cytotoxicity.[7] It should be noted, however, that no molecular rationalization has been made for the effect these heterocycles have on cytotoxicity.[2a]

Thus, the interest in lissoclinum peptides has been established. Studies in this area have resulted in new and improved synthetic methods and strategies for the construction of labile functionalities,[2a] as well as advances in structural determination methods.[10] Further studies into the factors responsible for biological activity and conformational geometry may one day lead to the rational design of 3-dimensionally preorganized macrocycles with selective metal-ion chelation or protein-binding properties.[7]

B. Strategies in the Synthesis of Lissoclinum Peptides

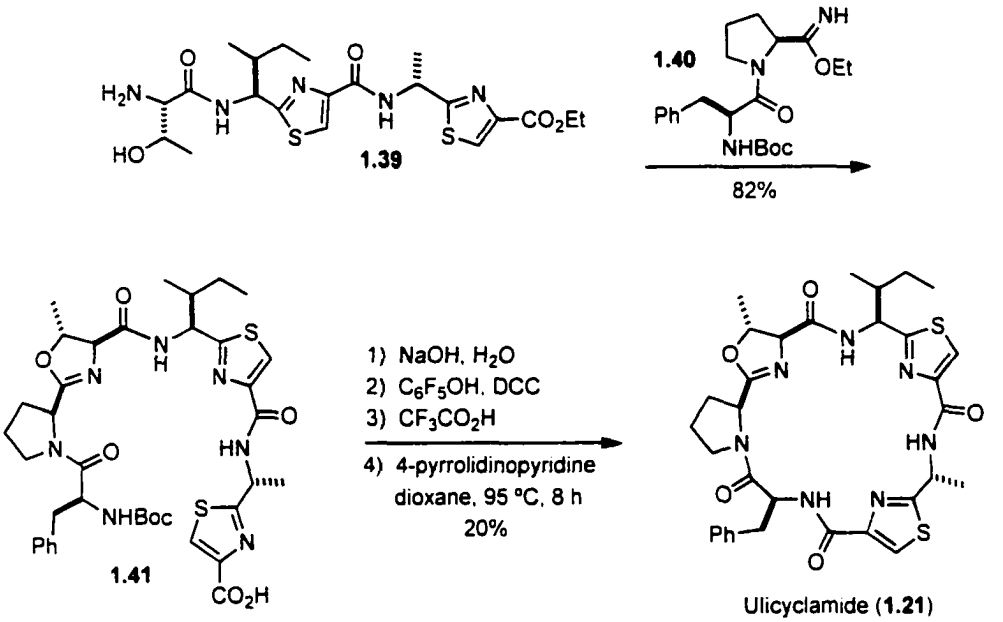
The strategy most frequently employed in the synthesis of lissoclinum peptides involves stepwise building of the constituent peptide sequence, followed by macrocyclization. The differences lie in whether or not each heterocyclic fragment is

brought in precyclized, or is realized after macrocyclization by dehydration of the requisite dipeptide components. The total synthesis of bistratamide C, delineated in Scheme 1.1, is an example wherein each azole subunit was introduced in heterocyclic form.[11] Oxazole **1.34** was obtained from oxazoline **1.33** by oxidation using either manganese dioxide or nickel dioxide, followed by acid-catalyzed cleavage of the nitrogen protecting group. Amide bond formation with valine-derived thiazole **1.35** was achieved using *iso*-butyl chloroformate, which provided the thiazole-oxazole sequence **1.36** in 82% yield after *N*-Boc removal. Chain extension with alanine-derived thiazole **1.37** proceeded in a similar manner to provide hexapeptide-based azole sequence **1.38**, which was cyclized to bistratamide C in varying yield upon heating in toluene. Alternative cyclization conditions, consisting of basic hydrolysis of the *C*-terminus followed by treatment with diphenylphosphoryl azide (DPPA) in DMF, provided **1.3** in 17% overall yield from N-Boc protected **1.36**.



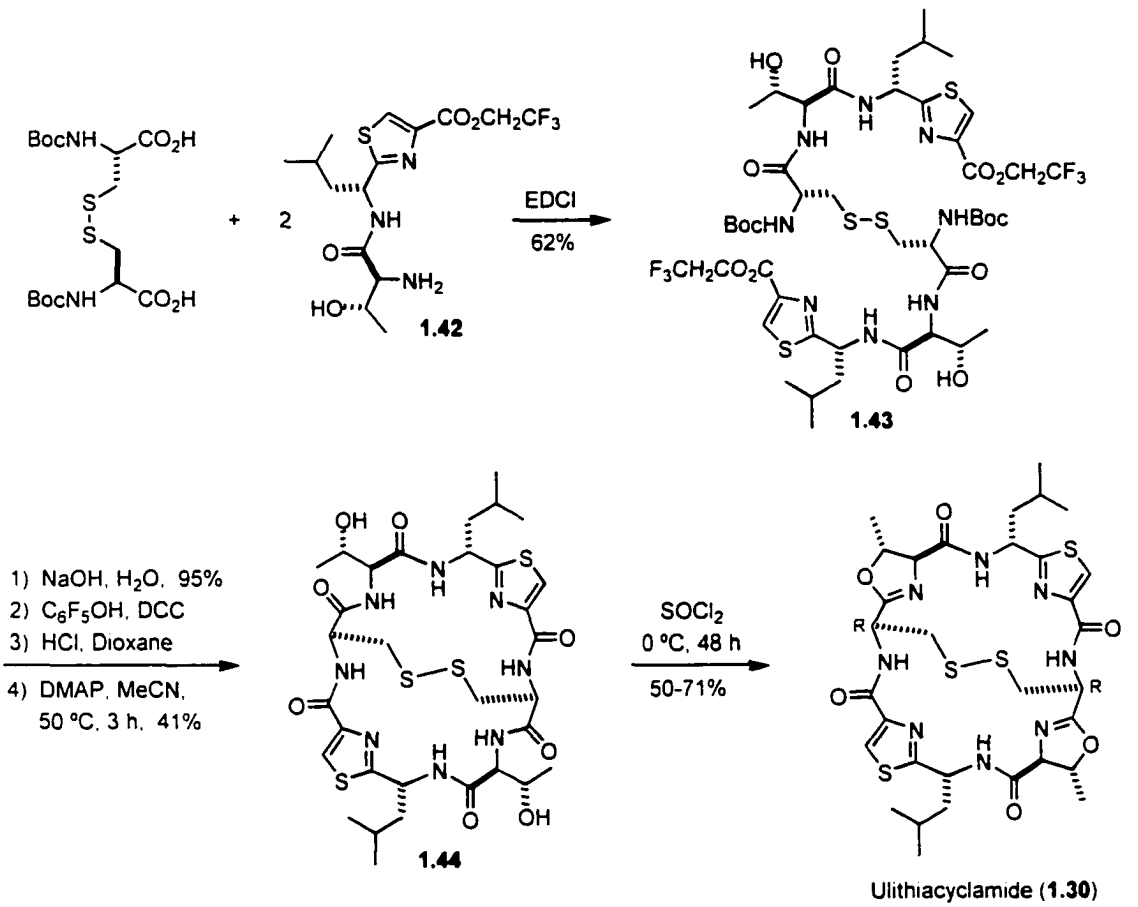
Scheme 1.1

A couple of examples have been reported in which azoline subunits were introduced with simultaneous peptide chain elongation.[12] This approach is based on the condensation of amino alcohols with imidic esters, as exemplified in the first-reported synthesis of a lissoclinum peptide, ulicyclamide (Scheme 1.2).[12a] Accordingly, the peptide chain **1.39**, containing a threonine-terminated bisthiazole sequence, was treated with the phenylalanine-proline derived imidate **1.40** to provide heptapeptide-based sequence **1.41** in 82% yield. The ethyl ester was hydrolyzed and replaced with the activating pentafluorophenyl ester using pentafluorophenol and dicyclohexyl-carbodiimide (DCC). After acidic cleavage of the Boc protecting group, the resultant amino ester was heated with 4-pyrrolidinopyridine in dioxane at 95 °C. Ulicyclamide (**1.21**) was thus obtained in 20% yield.



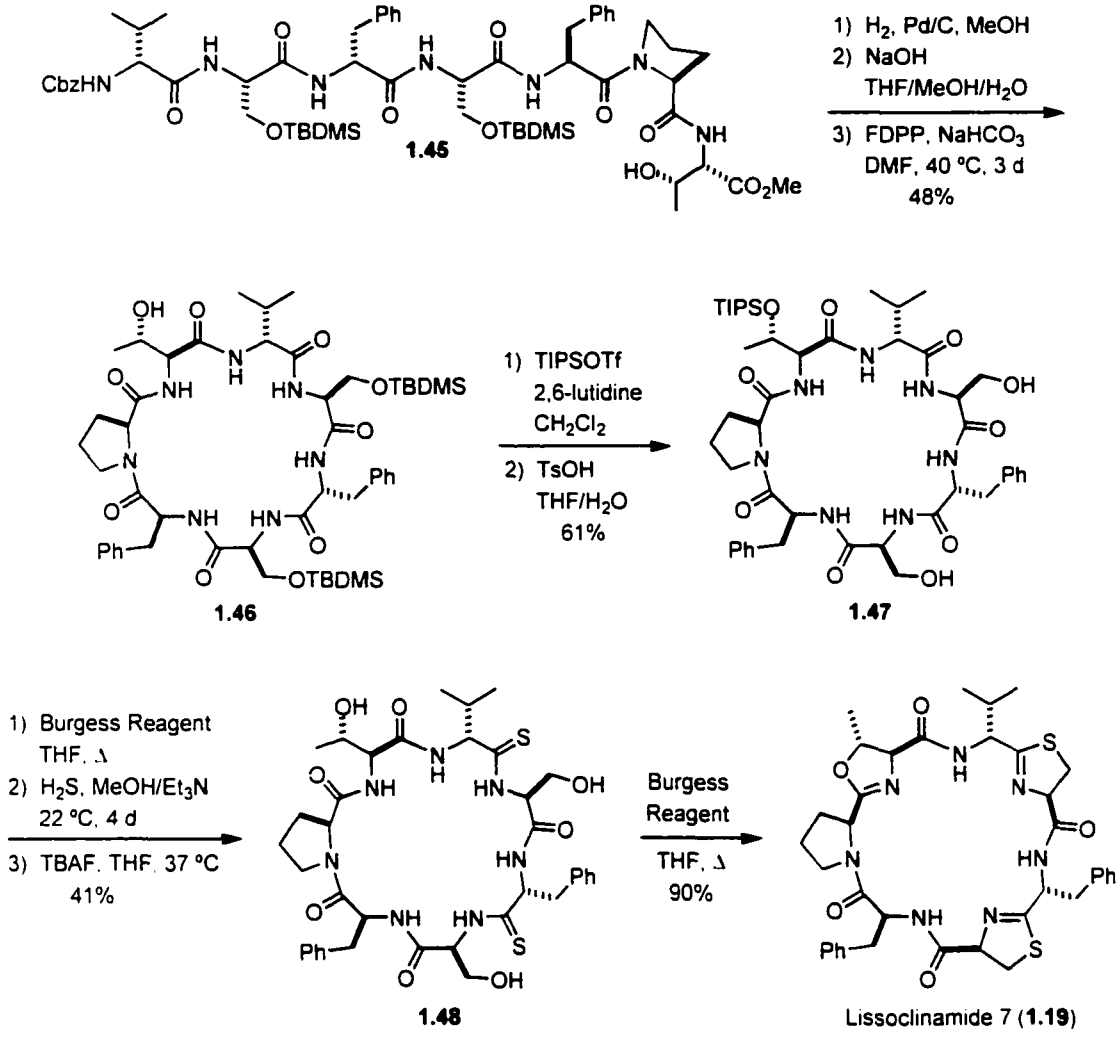
Scheme 1.2

Syntheses employing the imidate methodology carry the oxazoline moiety through a number of synthetic transformations. Because oxazoline and thiazoline segments are somewhat sensitive to acid-catalyzed hydrolysis (oxazolines),[13] or are



Scheme 1.3

quite sensitive to both acid- or base-catalyzed epimerization of the stereogenic centers exocyclic to C(2) and C(4) (thiazolines),[14] the constituent dipeptide sequences are more frequently cyclized to these 5-membered heterocycles after the macrocyclic ring closure has taken place.[2ab,14,15] One such example is demonstrated by the total synthesis of the most cytotoxic of the lissoclinum peptides, ulithiacyclamide (Scheme 1.3).[15a] Coupling of Boc-cysteine with two equivalents of L-*allo*-threonine-D-leucine-thiazole **1.42** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) led to the dimeric compound **1.43** in 62% yield. As before, the trifluoroethyl esters were exchanged for pentafluorophenyl esters, and the Boc groups were cleaved with HCl in dioxane. Tandem macrocyclization was effected by heating with 4,4-dimethylaminopyridine



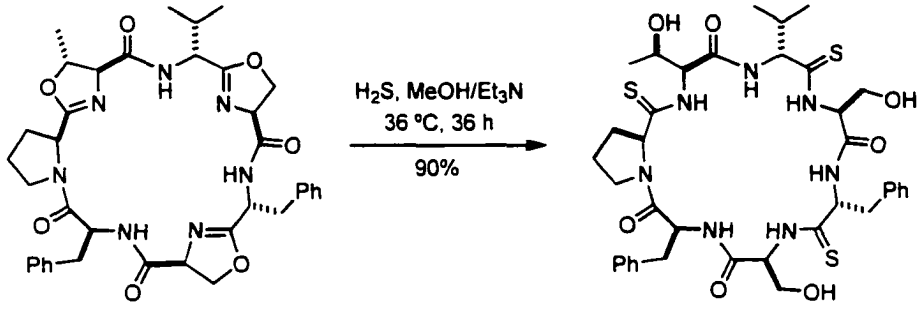
Scheme 1.4

(DMAP) in acetonitrile to provide compound **1.44** in 39% yield. *Ulithiacyclamide* (**1.30**) was realized in 50-71% yield after treatment with thionyl chloride.[15ab]

In instances for which more than one approach has been demonstrated in the total synthesis of a particular lissoclinum peptide, similar yields for ring closure have been obtained despite differences in retrosynthetic connection, or the presence or absence of some of the heterocyclic residues in the linear sequence.[14.2b] However, when readily-epimerized thiazoline segments are present, it becomes the method of choice to assemble the azoline segments last. The synthesis of lissoclinamide 7,

highlighted in Scheme 1.4, illustrates this approach.[14] Heptapeptide sequence **1.45**, with *tert*-butyldimethylsilyl ether-protected serine residues, was prepared for cyclization by hydrogenolysis with palladium on carbon, followed by saponification with aqueous base, to provide an intermediate amino acid. Treatment with pentafluorophenyl diphenylphosphinate (FDDP) in warm DMF gave the macrocycle **1.46** in 48% yield from **1.45**. Protection of the *allo*-threonine hydroxyl as the TIPS ether with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) served to prevent its cyclodehydration in a subsequent step. Cleavage of the TBDMS ethers with *para*-toluenesulfonic acid provided diol **1.47** in 61% yield. The next sequence of events utilized methodology developed by the Wipf group to interconvert oxazolines to thiazolines. First, the serine residues were cyclized to oxazolines upon treatment with Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$, inner salt).[16] Thiolysis of the oxazolines with H_2S was followed by cleavage of the silyl protecting group with tetrabutylammonium fluoride to provide bisthioamide **1.48** in 41% yield. The final step of the synthesis, entailing cyclization of the three azoline segments with Burgess reagent, proceeded in high yield.

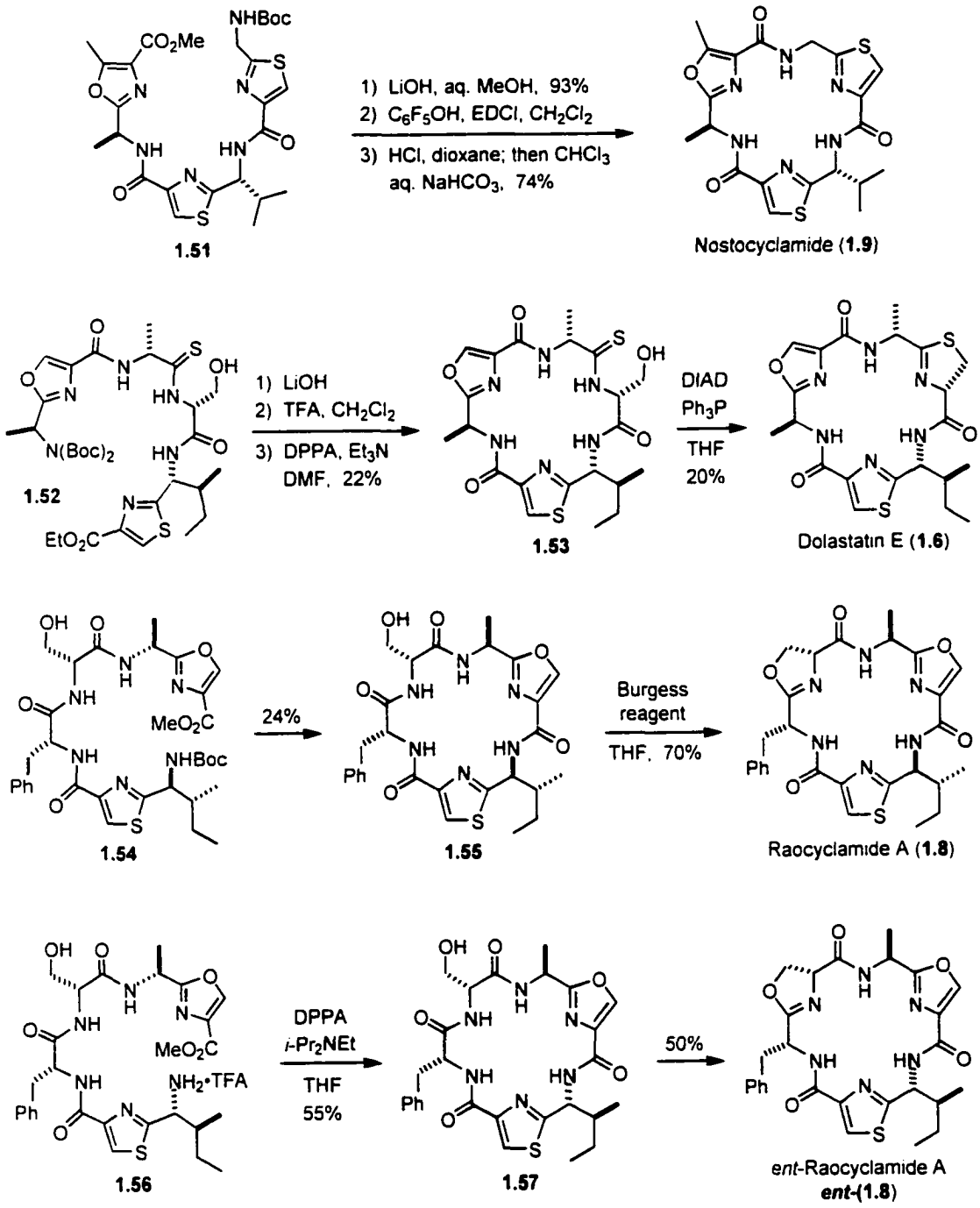
In this synthesis, protection and deprotection steps of the threonine hydroxyl could be avoided if thiolysis of compound **1.49**, below, were selective between the oxazoline derived from threonine, and those derived from serine. In fact, kinetic studies of simple model oxazolines showed thiolysis of the serine-derived one (similar to **1.33**, p 9) to be appreciably faster.[14] In the event, however, the authors found thiolysis of macrocycle **1.49** to be sluggish, and, under forcing conditions, trithioamide **1.50** was obtained in 90% yield. The lack of chemoselectivity indicates an increased stability of serine-derived oxazolines when embedded in a macrocyclic scaffold.



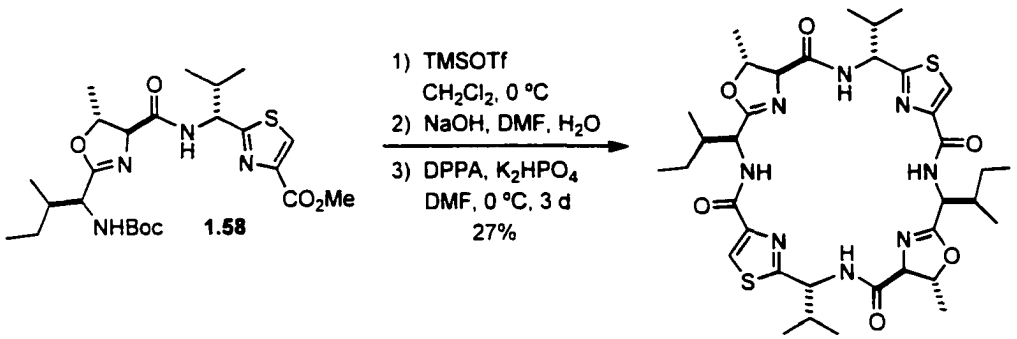
1.49 1.50

The macrocyclization steps from the syntheses of various class A peptides are shown in Scheme 1.5. Nostocyclamide (**1.9**) was realized from hexapeptide sequence **1.51** after basic hydrolysis, formation of the pentafluorophenyl ester, and acidic cleavage of the Boc group, in 69% yield.[2a] For the synthesis of dolastatin E, cyclic precursor **1.53** was obtained in 22% yield from hexapeptide **1.52** upon treatment of the intermediate amino acid with DPPA.[2a,3] Cyclization of the hydroxy thioamide functionality in **1.53** under Mitsunobu conditions provided dolastatin E (**1.16**) in 20% yield. A similar protocol provided pre-raocyclinamide A (**1.55**) from **1.54** in 24% yield, and the natural product **1.8** was realized in 70% yield after treatment of **1.55** with Burgess reagent.[15c] The originally-proposed structure for raocyclinamide A, consisting of the D-configuration at the isoleucine residue, was synthesized from **1.56** using the same sequence of events. Presuming that the deprotection steps in **1.54** to **1.55** were nearly quantitative, the macrocyclization yield for **1.56** was about twice that for precursor **1.54**. However, cyclodehydration to provide ***ent*-1.8** was less efficient than for the natural product. Together, these facts indicate the profound affect an apparently subtle stereochemical or conformational change can have on these reaction yields.

If the target macrocycle exhibits C_2-, C_3-, or C_4-symmetry, the most convergent approach to these types of cyclic peptides consists of the cyclodimerization, or oligimerization, of simple subunits. Two examples of this strategy applied to the

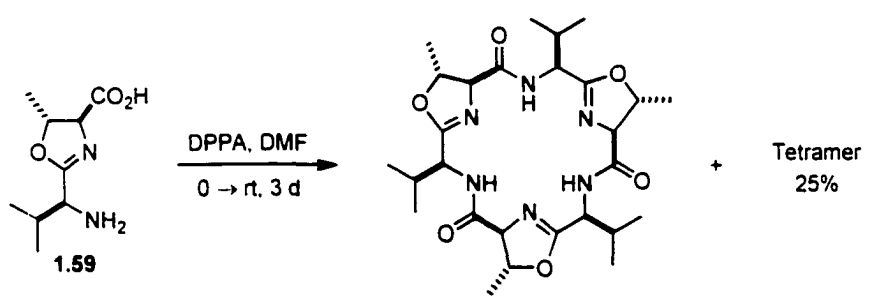


Scheme 1.5



Ascidiacyclamide (**1.23**)

synthesis of lissoclinum natural products are outlined below. In the first example, the total synthesis of ascidiacyclamide (**1.23**) was accomplished by cyclodimerization of the amino acid derived from oxazoline-thiazole monomer **1.58**.[13] The nonprotiolytic deprotection of the *N*-terminus was effected with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dry dichloromethane. The *C*-terminus was saponified with sodium hydroxide in aqueous DMF, and treatment with DPPA and potassium hydrogen phosphate in DMF provided the macrocycle in 27% yield from **1.58**. This synthesis served to establish the absolute configuration of this natural product.

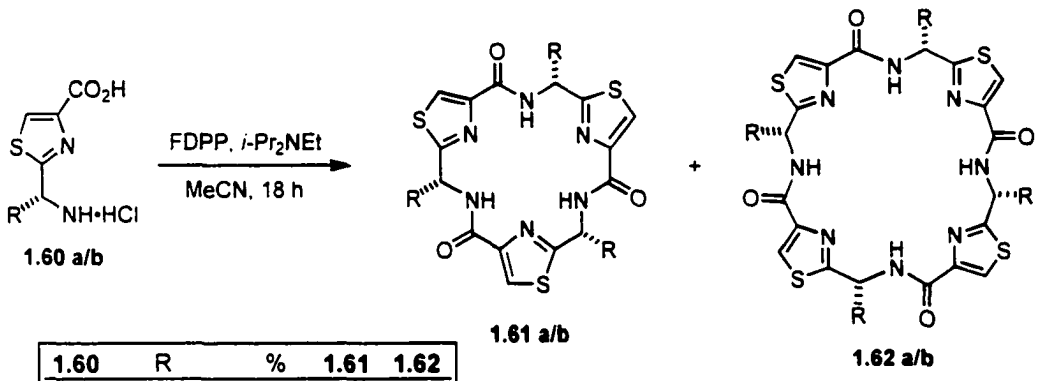


Westiellamide (**1.5**)
20%

In another example, a cyclotrimerization strategy was employed in the earliest reported synthesis of an 18-membered lissoclinum peptide, westiellamide.[17] Exposure of oxazoline **1.59** to DPPA provided the desired natural product **1.5** in 20% yield, accompanied by 25% of the tetramer. This approach was exploited after attempts to

cyclize the linear peptide sequence H-[Val-Thr(OTBS)]$_3$-X to cyclo-[Val-Thr(OTBS)]$_3$ failed under a variety of conditions. In this instance, the intact oxazoline moiety proved crucial to the success of macrocyclization.[17]

More recently, this approach has been used in the synthesis of some lissoclinum-type unnatural products for the purpose of producing libraries of compounds for the examination of conformational and metal-chelating properties, and of biological activity.[6] Another potential application of this strategy would be in creating templates or scaffolds for the synthesis of synthetic receptors or other macromolecular devices.[6]

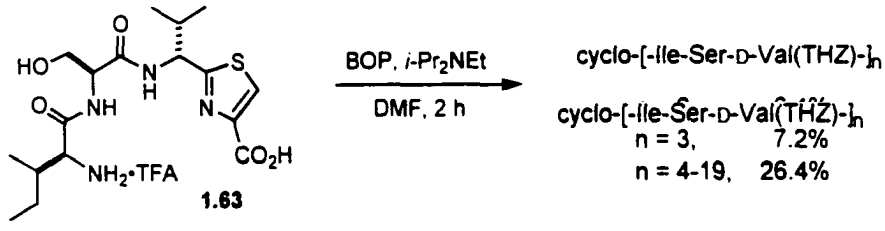


1.60	R	%	1.61	1.62
a	*i*-Pr	93	5	2
	(racemic)	75	1	1
b	CH_2Ph	10	0	1
	(racemic)	-	1	1

Oligomerization of optically pure thiazole **1.60a** provided 18-membered macrocycle **1.61a** and 24-membered **1.62a** in 93% yield as a 5:2 ratio.[6a] The ratio dropped to 1:1 when racemic thiazole **1.60a** was used. When the R group was benzyl (**1.60b**), very little tetramer **1.62b** was observed, and none of trimer **1.61b**. When racemic **1.60b** was oligomerized, macrocycles **1.61b** and **1.62b** were obtained as a nonstatistical mixture of diastereomers (yield was unspecified). It was suggested that the formation of trimeric product **1.61b** from oligomerization of enriched **1.60b** was

prevented due to the steric congestion that would be present if all the benzyl groups were on the same face of the trimeric product. In future work, the author planned to investigate the effect of different R groups in this regard.

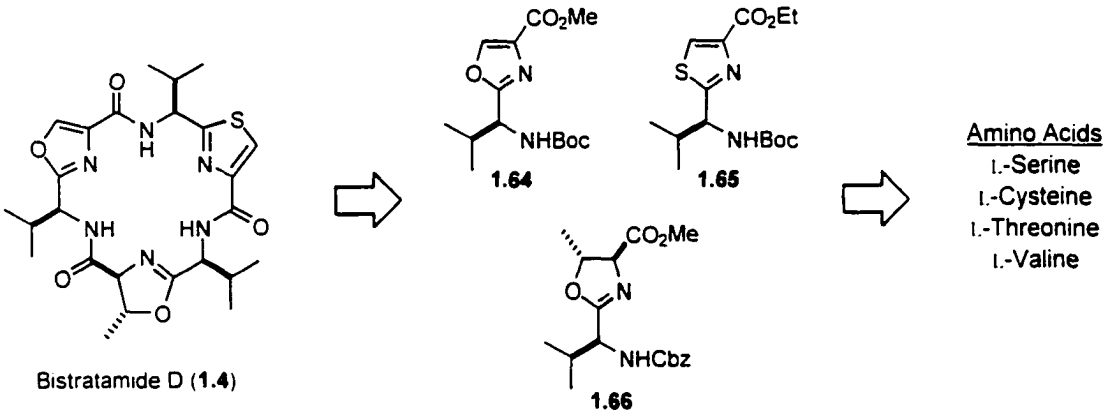
In a separate but similar example, involving the cyclooligomerization of the tetrapeptide sequence H-Ile-Ser-D-Val(THZ)-OH **1.63**, a concentration-dependent mixture of oligomers was obtained in moderate yield.[6b] Sequence **1.63** lacks the extra conformational constraint imparted by the oxazoline residue in protected tetrapeptide **1.58**, used in the cyclodimerization to produce ascidiacyclamide, which presumably accounts for the observed lack of selective oligomer formation. However, the presence of the pendant hydroxyl groups (from serine) provides the potential for further template elaboration.



The success of several of the approaches outlined here may stem from the presence of various conformation-restricting and turn-inducing modified amino acid residues in the peptide backbone.[2b] Specifically, both cyclized *trans*-oxazoline[2b,7] and alkyl-thiazole[6b] peptide derivatives are reported to be β-turn-inducing constraints in cyclic peptides. Despite this, steric congestion remains a factor in the synthesis of the class A peptides,[15c] such that the change in a single stereocenter can have a significant effect on the macrocyclization yield.[15c] or in the case of oligomerization reactions, the distribution[6a] of macrocyclic products obtained.

II. Results and Discussion

We turned our attention to the synthesis of the macrocyclic hexapeptide bistratamide D (**1.4**), isolated by Ireland and coworkers in 1992 from a Philippine collection of the ascidian *Lissoclinum bistratum*.[18] This compound is mildly cytotoxic, and induces depressant effects in mice when administered by intracerebral injection.



Scheme 1.6

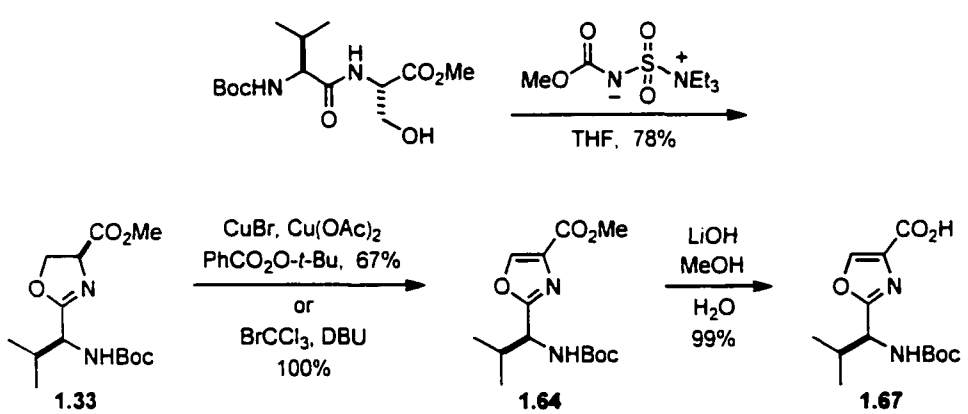
A. Retrosynthetic Analysis

The retrosynthetic approach to bistratamide D, consisting of disconnection at each of the amide linkages, and therefore similar to the one performed for bistratamide C,[11] is outlined in Scheme 1.6. This disconnection produces the oxazole **1.64**, thiazole **1.65**, and oxazoline **1.66** subunits shown, each of which may be derived from L-valine and another amino acid (**1.64**: serine, **1.65**: cysteine, **1.66**: threonine). The presence of the *trans*-4,5-disubstituted oxazoline **1.66** in the bistratamide D skeleton mandated the use of an amine protecting group other than BOC during the synthetic process. As discussed above, the *trans*-oxazoline ring is an acid-sensitive and readily opened moiety[13] and, for these reasons, it was decided to couple first the oxazole and thiazole

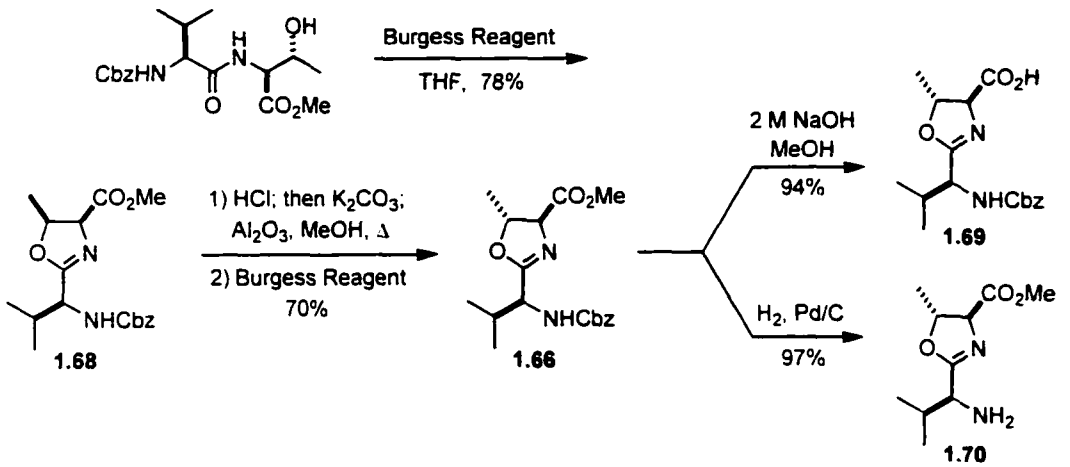
segments, followed by the preconstructed oxazoline, to generate a "linear" array of heterocycles. Bistratamide D would then arise through the macrocyclization of this sequence.

B. Synthesis of the Oxazoline, Oxazole, and Thiazole Fragments

Cyclodehydration of Boc-L-Val-Ser-OMe using Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$)[16] provided oxazoline **1.33**, which could be oxidized to oxazole **1.64** with MnO_2 or NiO_2 in 22-53% yield (Scheme 1.1).[11] Alternatively, use of a procedure[19] recently developed within the Meyers group allowed us to obtain oxazole **1.64** in 67% yield (Scheme 1.7). This procedure consists of heating oxazoline **1.33** with copper (I) bromide, copper (II) acetate, and *tert*-butylperoxybenzoate in benzene. It offers a high degree of reproducibility, being therefore much more reliable than the use of MnO_2 or NiO_2 for the oxidation of oxazolines. However, a quantitative yield of oxazole **1.64** was finally obtained through treatment of **1.33** with bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[20] Saponification of the ester functionality with lithium hydroxide in aqueous methanol gave the acid **1.67** in near quantitative yield.



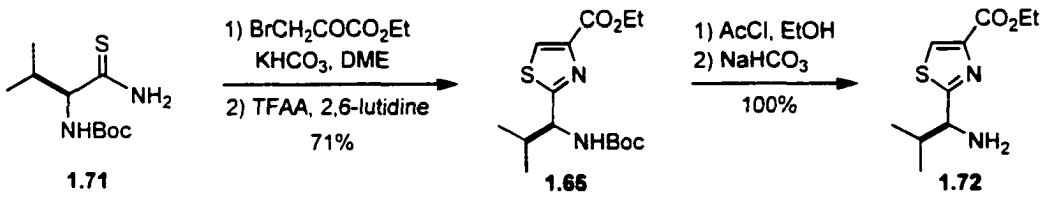
Scheme 1.7



Scheme 1.8

The *cis*-oxazoline **1.68** was obtained by Burgess reagent-promoted cyclodehydration of Cbz-L-Val-L-Thr-OMe as previously described,[21] wherein displacement of the activated tertiary hydroxyl group by the amide oxygen proceeded with inversion of stereochemistry (Scheme 1.8). Sequential treatment of **1.68** with 1 M HCl, K_2CO_3, and basic Al_2O_3 in MeOH at reflux hydrolyzed the oxazoline ring while maintaining the stereochemistry, to provide the hydroxyamide with the *allo*-threonine configuration (not shown).[22] A second cyclization with Burgess reagent gave the required *trans*-oxazoline fragment **1.66** in good yield (70%) from *cis*-oxazoline **1.68**. This protocol avoids the initial use of L-*allo*-threonine, which is about 200 times more expensive per gram than is L-threonine.[23] *trans*-Oxazoline **1.66** was readily deprotected to render acid **1.69** by hydrolysis with aqueous NaOH, or free amine **1.70** by palladium-catalyzed hydrogenolysis, in very good yields.

Although the Hantzsch synthesis of thiazoles is known to lead to epimerization at the chiral center adjacent to the 2-position,[2ab,24] use of Holzapfel's modified procedure,[24] as outlined in Scheme 1.9, allowed the acquisition of thiazole **1.65** with high optical purity. Treatment of L-valine-derived thioamide **1.71** with ethyl bromopyruvate and



Scheme 1.9

$KHCO_3$, followed by dehydration with trifluoroacetic anhydride and 2,6-lutidine, provided thiazole **1.65** in good yield. Optical purity was established as >99% by comparison to racemic material (made from DL-valine) using chiral HPLC (CHIRACEL OD column). Amine deprotection was achieved with acetyl chloride in absolute ethanol to provide primary amine **1.72** in quantitative yield.[25]

C. Fragment Couplings

As indicated in the retrosynthetic analysis of bistratamide D, it was of interest to join the oxazole and thiazole segments first. This was accomplished by forming mixed

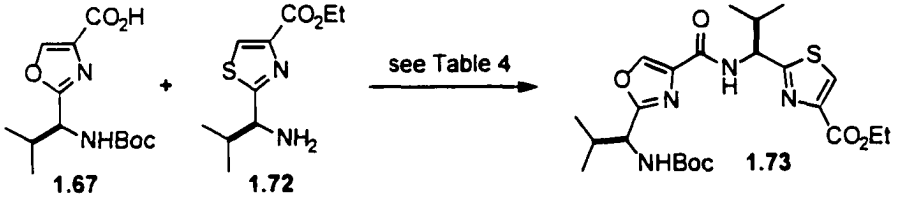
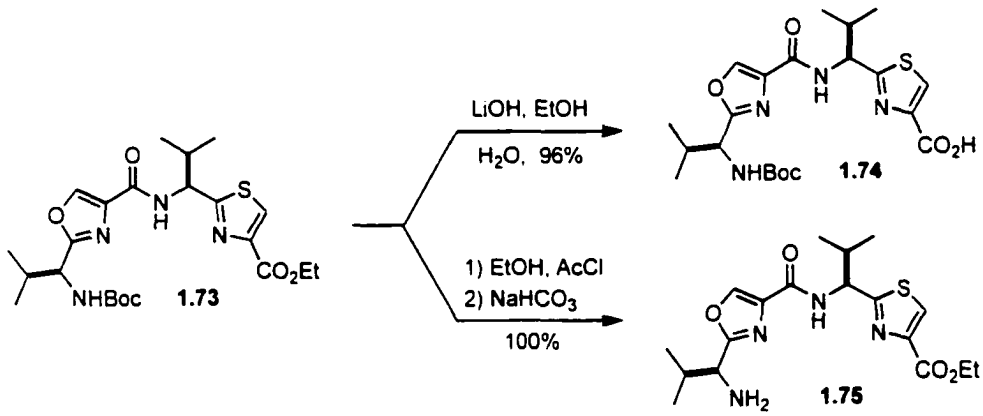


Table 1.4. Synthesis of Tetrapeptide **1.73**

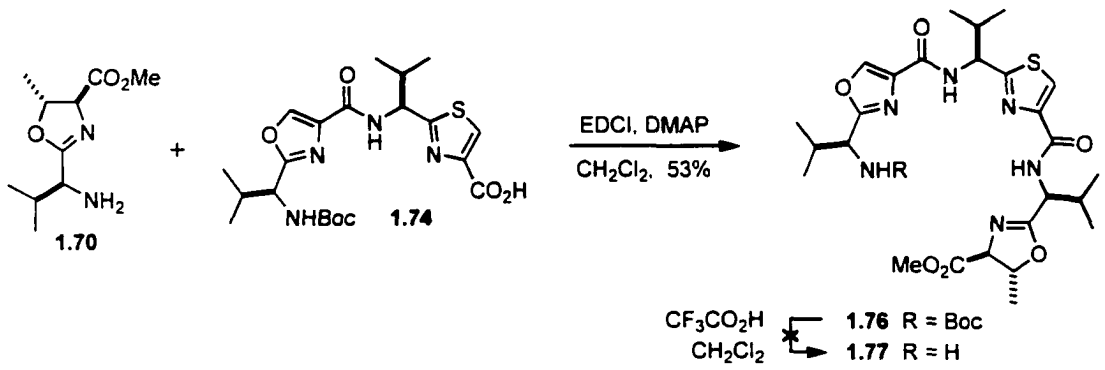
	Reagents	Yield of **1.73**	Side Product R-THZ-CO_2Et
a	*i*-BuO_2CCl, Et_3N, THF	36%	50% - CO_2-*i*-Bu
b	*i*-PrO_2CCl, Et_3N, THF	54%	14% - CO_2-*i*-Pr
c	*t*-BuOCCl, Et_3N, THF	73%	24% - CO-*t*-Bu
d	2,4,6-trichlorobenzoyl chloride, Et_3N, THF	53%	
e	DCC, CH_2Cl_2	35%	
f	CDI, THF	78%	
g	EDCI, HOBt, DMF	94%	

acyl carbonates of **1.67** with both isobutyl and isopropyl chloroformates, and via mixed anhydrides with both pivaloyl and 2,4,6-trichlorobenzoyl chloride. As shown in Table 1.4 (entries a-d), these resulted in low to moderate yields of the desired azole sequence **1.73**, often accompanied by large amounts of undesired side products derived from amine displacement at the more hindered carbonyl of the mixed carbonate or anhydride system (entries a-c). Activation of oxazole acid **1.67** with (1,1')-carbonyldiimidazole (CDI)[26] resulted in isolation of adduct **1.73** in 78% yield while use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of 1-hydroxybenzotriazole (HOBt) proved to be superior, finally providing **1.73** in 94% yield. The primary amine **1.75** or the carboxylic acid **1.74** could be obtained from **1.73** in almost quantitative yields by employment of conventional deprotection protocols (Scheme 1.10).



Scheme 1.10

To obtain the prerequisite "linear" sequence of heterocycles for the synthesis of bistratamide D, acid **1.74** was first coupled with oxazoline amine **1.70** (Scheme 1.11). This was accomplished in 53% yield by using EDCI and 4,4-dimethylaminopyridine (DMAP) in dichloromethane. However, amine deprotection of **1.76** did not yield the

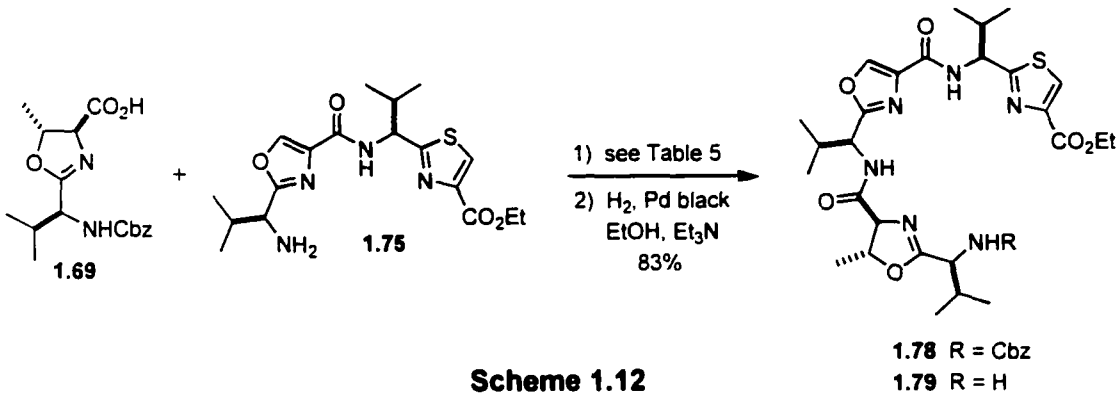


Scheme 1.11

amino ester **1.77**; only products derived from the opening of the oxazoline moiety were obtained.

This result prompted the exploration of the alternative coupling of oxazoline acid **1.69** with amine **1.75** (Scheme 1.12). Carboxyl activation of **1.69** via a mixed anhydride or the employment of dicyclohexylcarbodiimide (DCC) with DMAP failed to produce **1.78**. The use of EDCI with DMAP, 2-chloro-1,3-dimethyl-imidazolidium hexafluorophosphate (CIP) with 1-hydroxy-7-azabenzotriazole (HOAt),[27] or of triphenylphosphine with hexachloroacetone[28] did produce the hexapeptide **1.78** in a modest 31-40% yield (Table 1.5). However, the yield was dramatically improved to 79% by using EDCI with HOBt in DMF.

Removal of the Cbz group from compound **1.78** proved to be one of the critical steps of the synthesis. Any attempt to carry out an acid-catalyzed cleavage (BBr_3, trifluoroacetic acid, or bromocatecholborane) resulted in opening of the oxazoline moiety rather than in loss of the Cbz group. On the other hand, hydrogenolysis employing standard catalysts (10% Pd/C, $Pd(OH)_2$) in polar solvents (MeOH, EtOH, liquid ammonia[29]), or solvent mixtures ($EtOH/Et_3N$), and at elevated hydrogen pressure (80-100 psi), was a low-yielding (21-37%) alternative because of the poisoning effect of



Scheme 1.12

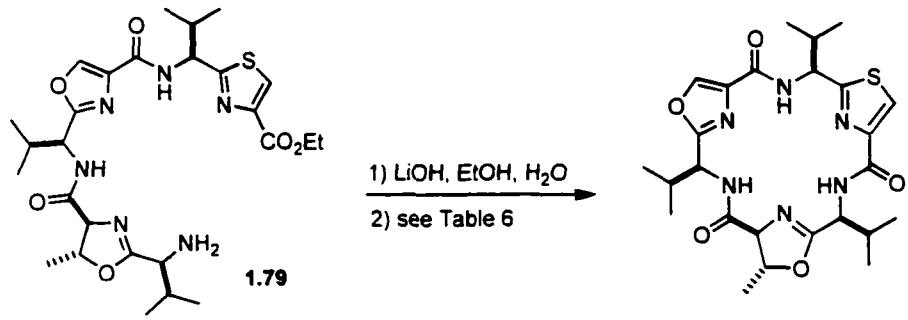
Table 1.5. Synthesis of Hexapeptide **1.78**

Reagents	Yield of **1.78**
EDCI, DMAP, DMF	36%
CIP, HOAt, *i*-Pr_2NEt, DMF	31%
PPh_3, Cl_3COCl_3, CH_2Cl_2	40%
EDCI, HOBt, DMF	79%

the sulfur-containing thiazole moiety. This problem was solved by using the more active catalyst Pd black to obtain amine **1.79** in 83% yield (Scheme 1.12).

D. Macrocyclization of Two Hexapeptide Sequences

Heating amine **1.79** in toluene for 3 days provided an unsatisfying 6% yield of bistratamide D (Table 1.6). Therefore, ester hydrolysis using lithium hydroxide in aqueous ethanol was followed immediately by macrolactamization via one of four sets of conditions. Use of bis-2-oxo-3-oxazolidinylphosphoryl chloride (BOP-Cl) provided bistratamide D in only 12% yield. Use of diphenylphosphoryl azide (DPPA) in DMF provided target product **1.4** in 39% yield, as did use of EDCI with HOBt. Finally, ester hydrolysis and treatment with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) and Hünigs base in DMF led to the isolation of bistratamide D (**1.4**) in 48% yield.



1.79

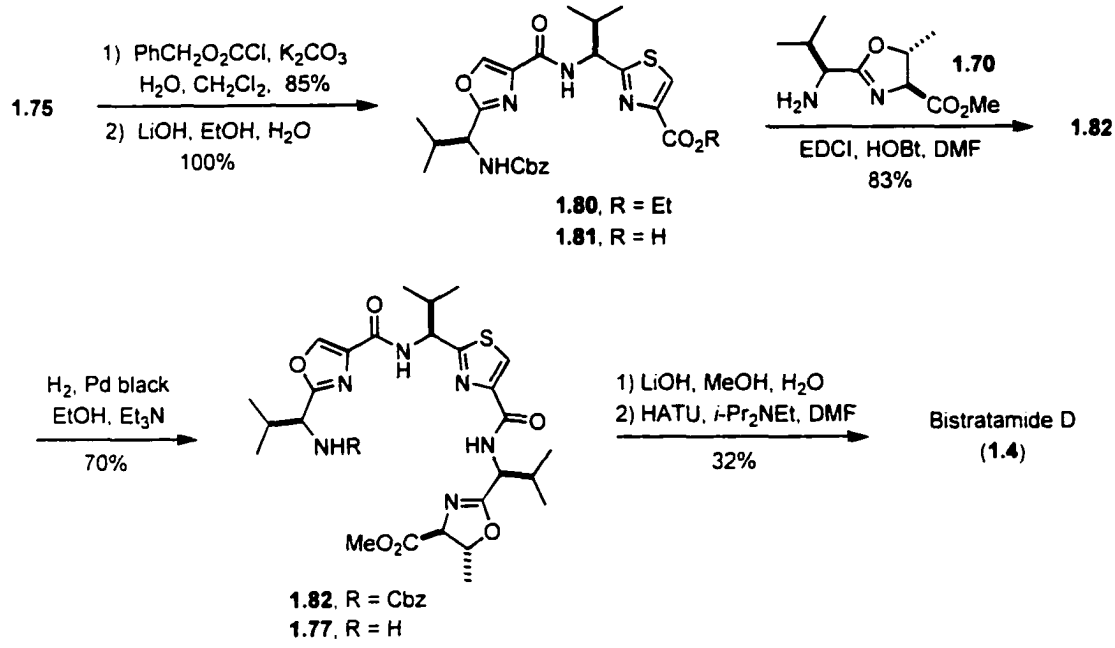
Bistratamide D (**1.4**)

Table 1.6. Cyclization of Hexapeptide Amine **1.79**

Reagents	Yield of **1.4**
Toluene	6%
BOPCl, *i*-Pr_2NEt, DMF	12%
DPPA, *i*-Pr_2NEt, DMF	39%
EDCI, HOBt, DMF	39%
HATU, *i*-Pr_2NEt, DMF	48%

As mentioned earlier, the first approach to bistratamide D, involving cleavage of the *N*-Boc protecting group from hexapeptide **1.76**, was unsuccessful. In the second approach, described above, a reliable method to cleave the *N*-Cbz group from hexapeptide **1.78** had been developed, despite the presence of the sensitive oxazoline, and the palladium-poisoning thiazole, moieties. Given the recent enlightenment in these matters, it was felt that further study of the first route, involving a change in protecting group for tetrapeptide **1.74**, could overcome the earlier failure.

If amine **1.75** were reprotected as the *N*-Cbz derivative **1.80**, using benzyl chloroformate, and then the ester hydrolyzed to provide new acid **1.81**, it seemed a sequence would be in hand that could later be *N*-deprotected (Scheme 1.13). This indeed turned out to be the case. Coupling of oxazoline amine **1.70** with acid **1.81**, using EDCI and HOBt, proceeded in good yield (83%) to provide hexapeptide **1.82**, which was smoothly hydrogenolyzed to provide previously inaccessible



Scheme 1.13

amine **1.77**, in 70% yield, using the conditions described for **1.78** to **1.79**. Amine **1.77** was then carried on, after ester hydrolysis, to bistratamide D in 32% yield using HATU as before.

Early on, it was suspected that cyclization of precursor **1.77** might be lower yielding than for cyclization of **1.79**. Although the bulk of the amine terminus is essentially the same in both fragments, the steric environment of the carboxy termini are rather different. In **1.77**, the R group on the carboxy terminus, namely the oxazoline, presents the opportunity for eclipsing interactions to occur as the carbonyl hybridization changes from sp^2 to sp^3 during the course of reaction. However, the planar thiazole in **1.79** would display no such interactions. Indeed, precursor **1.77** provided bistratamide D in 32% yield, while the yield of **1.4** was 48% from **1.79**.

In summary, the first total synthesis of bistratamide D has been accomplished wherein employment of EDCI with HOBt for segment coupling proved to be superior to other coupling methods explored. The present approach provided ready access to the

two hexapeptide sequences **1.78** and **1.82**, cyclization of which with HATU led to the final compound in moderate, but typical, yields for macrocyclizations of this type.[30]

III. Experimental

General Methods: All ^1H NMR spectra were recorded at 300 MHz and data were reported as follows: chemical shifts, in parts per million referenced to either the internal chloroform ($CHCl_3$) peak (7.27 ppm), or to the internal methanol (CH_3OH) peak (pentet, 3.31), (multiplicity, coupling constant(s), number of protons). ^{13}C NMR and DEPT spectra were recorded at 75 MHz. Chemical shifts were referenced to the central peak of either the $CDCl_3$ triplet (77.0 ppm) or the CD_3OD septet (49.2 ppm). Low resolution mass spectra (GC-MS) were obtained with a Hewlett-Packard model 5890 instrument equipped with a Hewlett-Packard 5970B mass selective detector (ionization potential 70 eV). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia. Optical rotations were determined with a Rudolph Research Autopol III instrument and were referenced to the D-line of sodium (598 nm). Melting points were measured in open Pyrex capillary tubes and are uncorrected. Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230-400 mesh), (60 Å). Radial chromatography was carried out on a Harrison Research Chromatron 7924 and silica gel plates (N° 7749, Kieselgel 60 PF 254, Merck). With TLCs, compounds were visualized by UV light (254 nm), or by using potassium permanganate or Ninhydrin stain.

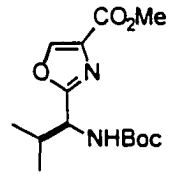
All nonaqueous reactions were conducted under an argon atmosphere in flame-dried apparatus. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Concentrations were performed under reduced pressure with a rotary evaporator.

Solvents: Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. Dichloromethane and benzene were

distilled from calcium hydride. Tetrahydrofuran and dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. N,N'-Dimethylformamide was distilled from calcium hydride under reduced pressure (< 20 mmHg), and triethylamine was stored over KOH.

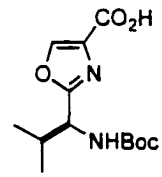
Compounds: Commercially available copper (I) bromide was purified by refluxing in dry THF, decanting the liquid, and repeating the procedure until a colorless supernatant was obtained. Methyl *N*-((triethylammonio)sulfonyl)carbamate (Burgess reagent), prepared according to literature procedures,[16] was stored in brown bottles under argon at -20 °C and checked by NMR spectroscopy prior to each use.

Oxazoline **1.33** was prepared as previously described.[11] *cis*-Oxazoline **1.68** was prepared as described by Wipf.[21] Thioamide **1.71** was synthesized following the procedure described by Holzapfel.[24] All other reagents were commercially available (Aldrich) and used without any further purification.



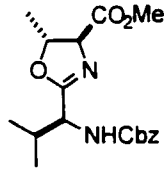
2-[(S)-1'-*tert*-Butyloxycarbonylamino-2'-methylpropyl]-4-carbomethoxy-oxazole 1.64. Oxazoline **1.33**[11] (1.67 g, 5.56 mmol), dissolved in CH_2Cl_2 (56 mL), was cooled to 0 °C in an ice bath. DBU (0.91 mL, 6.08 mmol) was added, followed by addition of $BrCCl_3$ (0.71 mL, 7.20 mmol), dropwise. The resulting mixture was allowed to stir overnight while warming to room temperature. The reaction was washed with saturated (aqueous) NH_4Cl (2 x 27 mL), and the aqueous phase was extracted with EtOAc (2 x 14 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to provide 1.66 g (100%) of **1.64** as a yellow solid that required no further

purification: mp 120-124 °C; R_f = 0.68 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ -44.4 (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.84 (app t, *J* = 6.4 Hz, 6H), 1.34 (s, 9H), 2.12 (m, 1H), 3.82 (s, 3H), 4.71 (dd, *J* = 6.3 Hz and 9.2 Hz, 1H), 5.30 (br d, *J* = 9.5 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.8, 28.3, 32.9, 52.2, 54.4, 80.0, 133.2, 144.0, 155.4, 161.6, 165.2; IR (neat) 3353, 1714 cm^{-1}; MS *m/z* 298. Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.31; H, 7.43; N, 9.31.

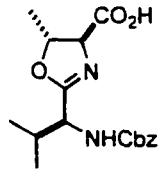


4-[2-[(S)-1'-*tert*-Butyloxycarbonylamino-2'-methylpropyl]]-oxazole Carboxylic Acid 1.67. Lithium hydroxide monohydrate (95 mg, 2.26 mmol) was added to a stirred solution of oxazole ester **1.64** (0.29 g, 0.97 mmol) in 4 mL of MeOH/H_2O (3:1) at 0 °C and stirred for 1 h with gradual warming to room temperature. TLC monitoring showed complete consumption of starting material. The solvents were concentrated, and the residue partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was separated, and the aqueous phase was acidified to pH 2 with 1 M HCl and then extracted with EtOAc (4 x 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give 274 mg (99%) of **1.67** as a pale yellow solid that was used without purification: mp 154-155 °C; R_f = 0.12 (CH_2Cl_2/MeOH 95:5); $[\alpha]^{23}_D$ -28.9 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 9H), 2.17 (m, 1H), 4.82 (app t, *J* = 8.2 Hz, 1H), 6.41 (d, *J* = 9.8 Hz, 1H), 8.28 (s, 1H), 12.44 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5, 19.1, 28.5, 33.0, 54.8, 80.2,

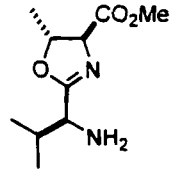
133.4, 144.9, 156.2, 163.9, 167.1; IR (neat) 3314, 3107, 2552, 1745 cm^{-1}; MS *m/z* 284; HRMS calcd for $C_{13}H_{20}N_2O_5$ 284.13722, found 284.13720.



2-(1'-Benzyloxycarbonylamino-2'-methylpropyl)-4-carbomethoxy-5-methyl-*trans*-oxazoline 1.66. To *cis*-oxazoline **1.68**[21] (4.20 g, 12.1 mmol) in 200 mL THF was added 1 M HCl (aqueous) (80 mL), and the mixture stirred 30 min. The solution was then made alkaline (pH 9) by addition of solid K_2CO_3. The THF was evaporated, the residue extracted with EtOAc (3 x 150 mL), and the combined organic phases were concentrated. To the residue were added MeOH (150 mL) and basic alumina (10.0 g, 98.0 mmol), and the mixture was heated to reflux for 4 h. The mixture was cooled to room temperature, sonicated for 5 min, and then vacuum filtered to remove the alumina. The filtrate solvent was concentrated and the residue was dissolved in THF (200 mL). Burgess reagent (3.16 g, 13.2 mmol) was added and the solution was heated at 80 °C in a pressure tube for 3 h. The mixture was cooled, the solvent concentrated, and the residue purified by chromatography to provided 2.95 g (70%) of **1.66** as a clear oil, whose spectroscopic data were in agreement with those reported by Wipf:[17] R_f = 0.29 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ +62.5 (*c* 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 5.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.43 (d, *J* = 6.2 Hz, 3H), 2.14 (m, 1H), 3.77 (s, 3H), 4.27 (d, *J* = 7 Hz, 1H), 4.42 (m, 1H), 4.85 (m, 1H), 5.11 (m, 2H), 5.47 (d, *J* = 9.2 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.4, 19.0, 21.1, 32.0, 52.8, 54.6, 67.2, 74.3, 80.0, 128.3, 128.3, 128.7, 136.6, 156.4, 169.2, 171.5; IR (neat) 3370, 3221, 1721 cm^{-1}.

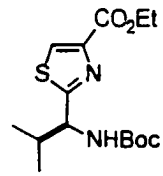


4-[2-(1'-Benzyloxycarbonylamino-2'-methylpropyl)]-5-methyl-*trans*-oxazoline Carboxylic Acid 1.69. A solution of **1.66** (360 mg, 1.03 mmol) in MeOH (3 mL) was treated with 2 M NaOH (0.57 mL, 1.14 mmol) at 0 °C. After 1 h, the solvent was evaporated *en vacuo* and the residue was partitioned between water and CH_2Cl_2. The phases were separated, and the aqueous layer was acidified and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were evaporated to give 324 mg (94%) of **1.69** that was used without further purification: $[\alpha]^{23}_D$ -2.3 (*c* 0.80, MeOH); ^{1}H NMR (CD_3OD) δ 0.92 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.40 (d, *J* = 7.1 Hz, 3H), 2.14 (m, 1H), 3.61 (d, *J* = 5.5 Hz, 1H), 4.13 (d, *J* = 5.9 Hz, 1H), 5.09 (s, 2H), 5.33 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (CD_3OD) δ 17.8, 18.3, 19.6, 31.9, 60.0, 61.1, 67.8, 71.6, 128.9, 129.1, 129.5, 138.1, 158.9, 170.9, 172.1; IR (neat) 3404, 1736, 1702, 1654, 1640 cm^{-1}.



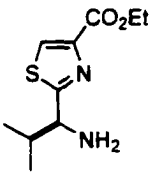
2-(1'-Amino-2'-methylpropyl)-4-carbomethoxy-5-methyl-*trans*-oxazoline 1.70. A solution of **1.66** (124 mg, 0.36 mmol) in MeOH (2 mL) was hydrogenated over 15 mg of 5% Pd/C. After 2 h, the reaction mixture was filtered over Celite and evaporated to yield 75 mg (97%) of crude **1.70** that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 6H), 1.42 (d, *J* = 6.4 Hz, 3H), 2.02 (m, 1H), 3.44

(d, J = 5.2 Hz, 1H), 3.76 (s, 3H), 4.25 (d, J = 5.7 Hz, 1H), 4.84 (m, 1H); IR (neat) 3379, 3303, 2965, 1730, 1654 cm^{-1}.

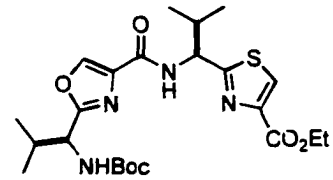


2-[(*S*)-1'-tert-Butyloxycarbonylamino-2'-methylpropyl]-4-carboethoxy-thiazole 1.65, was prepared using Holzapfel's procedure.[24] Thioamide **1.71**[24] (0.50 g, 2.15 mmol) and $KHCO_3$ (1.72 g, 17.2 mmol) were stirred vigorously in 13 mL of DME for 8 min at room temperature. Ethyl bromopyruvate (0.81 mL, 6.45 mmol) was added via syringe and the mixture stirred at room temperature for 45 min before being cooled to 0 °C in an ice bath. A solution of trifluoroacetic anhydride (1.21 mL, 8.58 mmol) and 2,6-lutidine (2.12 mL, 18.3 mmol) in 3.3 mL of DME was transferred to the mixture dropwise via cannula over a period of 10 min. After the addition was complete, the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The solvents were concentrated, and the residue partitioned between H_2O (25 mL) and EtOAc (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (EtOAc/hexanes 5:1) followed with ninhydrin stain gave, after recrystallization ($CHCl_3$/hexanes), 0.50 g (71%) of **1.65** as white solid: mp 116-117 °C; R_f = 0.81 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ -37.1 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H), 2.39 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.85 (m, 1H), 5.30 (br d, J = 9 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.0, 19.2, 28.0, 33.0, 57.8, 61.1, 79.7, 126.6, 147.1, 155.2, 161.1, 173.0; IR ($CDCl_3$) 3350, 3097, 1712, 1477 cm^{-1}; MS m/z 285, 229, 185; HRMS

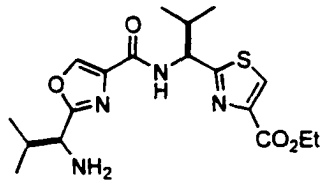
calcd for $C_{15}H_{24}N_2O_4S$ 328.14568, found 328.14576. Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.85; H, 7.36; N, 8.53. Found: C, 54.58; H, 7.51; N, 8.49.



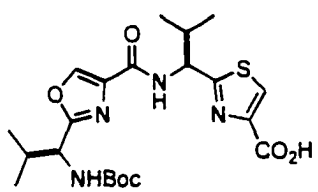
2-[(*S*)-1'-Amino-2'-methylpropyl]-4-ethoxycarbonyl-thiazole 1.72. Acetyl chloride (2.5 mL, 35.3 mmol) was added dropwise to absolute ethanol (17 mL) at 0 °C. Thiazole **1.65** (1.16 g, 3.53 mmol) was added as a solid in one portion and the solution allowed to stir overnight at room temperature. Concentration of the reaction mixture gave 0.93 g (100%) of **1.72**•HCl as a white foam. Pure material was obtained by partitioning the crude material between CH_2Cl_2 (5 mL) and saturated (aqueous) $NaHCO_3$ (5 mL). The phases were separated, and the organic phase dried (Na_2SO_4) and concentrated to provide the free amine **1.72** as a colorless oil: R_f = 0.18 (EtOAc); $[\alpha]^{23}_D$ -24.4 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 2.02 (br s, 2H), 2.27 (m, 1H), 4.19 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 17.0, 19.8, 34.8, 59.6, 61.6, 127.4, 147.2, 161.9, 191.2; IR (neat) 3387, 3318, 3116, 1728, 1618 cm^{-1}; HRMS calcd for $C_{10}H_{16}N_2O_2S$ 228.09325, found 228.09315.



***N*-Boc-oxazole-thiazole-ethyl Ester 1.73.** *To* thiazole amine **1.72** (0.20 g, 0.88 mmol) in DMF (13 mL) at -10 °C were added 1-hydroxybenzotriazole (0.38 g, 2.81 mmol) and oxazole acid **1.67** (0.28 g, 0.98 mmol), and this was stirred at -10 °C for 20 min. EDCI (0.20 g, 1.05 mmol) was added and the mixture stirred at room temperature for 21 h. After this time, the reaction mixture was diluted with 26 mL EtOAc, and 13 mL brine was added. The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 26 mL). The organic phases were then washed successively with 10% citric acid (2 x 13 mL), saturated (aqueous) $NaHCO_3$ (2 x 13 mL), and brine (2 x 13 mL) and then dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 2:1) gave 0.41 g (94%) of **1.73** as a white solid: mp 144.5-145.8 °C; R_f = 0.40 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ -49.0 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91-1.00 (m, 12H), 1.34-1.42 (m, 12H), 2.15 (m, 1H), 2.57 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.75 (m, 1H), 5.15 (br d, *J* = 9.1 Hz, 1H), 5.26 (m, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 8.06 (s, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 18.1, 18.3, 18.9, 19.8, 28.5, 32.8, 33.2, 54.4, 56.2, 61.6, 80.3, 127.1, 135.7, 141.5, 147.7, 155.5, 160.4, 161.4, 164.1, 171.4; IR ($CDCl_3$) 3325, 3127, 1716, 1596, 1505 cm^{-1}; HRMS calcd for $C_{23}H_{34}N_4O_6S$ 494.21991, found 494.22019. Anal. Calcd for $C_{23}H_{34}N_4O_6S$: C, 55.85; H, 6.93; N, 11.33. Found: C, 55.93; H, 6.87; N, 11.27.

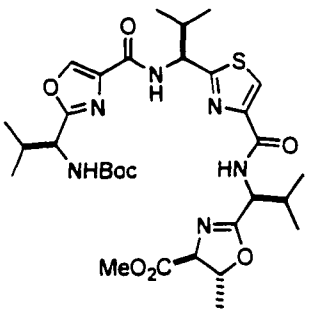


Aminooxazole-thiazole-ethyl Ester 1.75. Acetyl chloride (2.51 mL, 35.3 mmol) was added dropwise to absolute ethanol (20 mL) at 0 °C. t-Boc **1.73** (666 mg, 1.35 mmol) was added to the solution, and the mixture was stirred at room temperature overnight. Evaporation of the solvents in vacuo provided 579 mg of **1.75**•HCl (100%) as a white solid. A portion of the compound was dissolved in CH_2Cl_2 and saturated (aqueous) $NaHCO_3$ was added; the organic layer was separated, dried over Na_2SO_4, filtered and evaporated to provide **1.75** as the free amine: R_f = 0.20 (EtOAc); $[\alpha]^{25}_D$ -31.4 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87-0.99 (m, 12H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.76 (bs, 2H), 2.05 (m, 1H), 2.55 (m, 1H), 3.46 (d, *J* = 5.7 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 5.25 (dd, *J* = 7.0 Hz and 9.2 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 8.02 (s, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.7, 18.0, 18.9, 19.5, 33.0, 33.3, 55.7, 56.0, 61.3, 126.8, 135.2, 141.0, 147.3, 160.3, 161.1, 167.0, 171.2; IR (film) 3568, 3405, 1728, 1668, 1596 cm^{-1}.



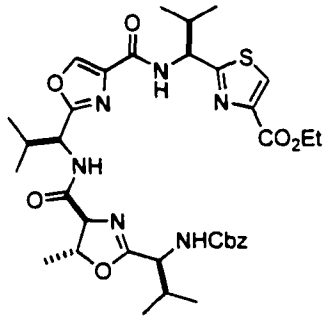
N-Boc-oxazole-thiazole Carboxylic Acid 1.74. Lithium hydroxide mono-hydrate (19 mg, 0.43 mmol) was added to a solution of **1.73** (100 mg, 0.20 mmol) in 4 mL of EtOH/H_2O (3:1). After 1 h, the solvents were concentrated and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was separated and the

aqueous layer was acidified and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were evaporated to give 90 mg (96%) of **1.74** as a solid: mp 164-166 °C; R_f = 0.21 (CH_2Cl_2/EtOAc 95:5); $[\alpha]^{25}_D$ -54.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81-1.07 (m, 12H), 1.39 (s, 9H), 2.10-2.24 (m, 1H), 2.48-2.63 (m, 1H), 4.75 (bs, 1H), 5.12-5.35 (m, 2H), 7.62 (d, *J* = 9.1 Hz, 1H), 8.13 (s, 2H), 10.14 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.1, 18.6, 19.5, 28.2, 32.5, 32.9, 54.2, 56.0, 80.1, 128.2, 135.2, 141.6, 146.8, 155.3, 160.4, 163.6, 164.1, 171.4; IR (film) 3310, 1709, 1693, 1678, 1666 cm^{-1}. This material was used in the next step without further purification.



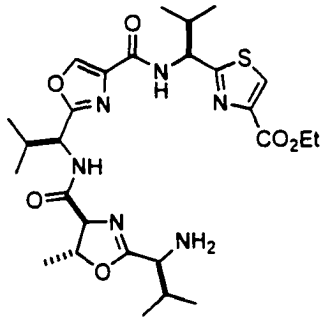
N-Boc-oxazole-thiazole-oxazoline-methyl Ester 1.76. EDCI (150 mg, 0.78 mmol) was added to a solution of **1.70** (186 mg, 0.87 mmol) and **1.74** (365 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) at 0 °C. A catalytic amount of DMAP was then added. The reaction was allowed to warm to room temperature, and after 3 h, water was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give 275 mg (53%) of **1.76**: ^{1}H NMR ($CDCl_3$) δ 0.89-1.03 (m, 18H), 1.41 (s, 9H), 1.41 (d, *J* = 6.1 Hz, 3H), 2.16-2.29 (m, 1H), 2.48-2.59 (m, 1H), 3.75 (s, 3H), 4.28 (d, *J* = 6.8 Hz, 1H), 4.75-4.84 (m, 3H), 5.09 (d, *J* = 8.6 Hz, 1H), 5.29 (dd, *J* = 6.3 Hz and 9.2 Hz, 1H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 9.1 Hz, 1H), 7.99 (s, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$)

δ 17.7, 17.8, 18.0, 18.7, 18.8, 19.5, 20.8, 28.2, 31.8, 32.4, 32.7, 52.3, 52.4, 54.3, 55.9, 74.2, 79.3, 80.7, 123.3, 135.4, 141.3, 149.6, 155.2, 160.2, 160.6, 163.8, 168.4, 171.1, 171.3.

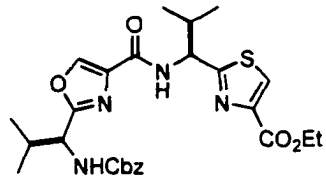


N-Cbz-oxazoline-oxazole-thiazole-ethyl Ester 1.78. Amine **1.75** (504 mg, 1.28 mmol) and acid **1.69** (428 mg, 1.28 mmol) were dissolved in toluene, and then the solution was concentrated. DMF (18 mL) was added, the solution cooled to -10 °C, and HOBt (553 mg, 4.10 mmol) was added. This was stirred for 20 min at -10 °C before EDCI (294 mg, 1.54 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 14 h, after which the solvent was evaporated under reduced pressure and the residue partitioned between EtOAc (40 mL) and brine (20 mL). The phases were separated, and the aqueous phase extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed successively with 10% citric acid (2 x 10 mL), saturated (aqueous) $NaHCO_3$ (2 x 10 mL), and brine (2 x 10 mL), dried ($MgSO_4$), and concentrated. Radial chromatographic purification of the crude residue provided 718 mg (79%) of **1.78** as a light yellow foam: R_f = 0.16 (hexanes/EtOAc 1:1); $[\alpha]^{25}_D$ -5.53 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80-0.97 (m, 18H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.41 (d, *J* = 6.1 Hz, 3H), 2.04-2.19 (m, 2H), 2.46-2.55 (m, 1H), 4.15 (d, *J* = 7.4 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.73 (m, 1H), 4.95-5.07 (m, 3H), 5.23 (dd, *J* = 7.1 Hz and 9.1 Hz, 1H),

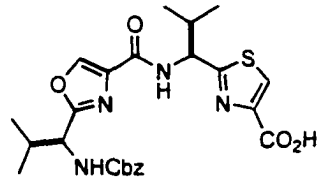
5.59 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 9.1 Hz, 1H), 7.25 (m, 5H), 7.58 (d, J = 9.1 Hz, 1H), 8.00 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.7, 17.9, 18.0, 18.6, 18.7, 19.4, 21.6, 31.3, 31.9, 32.9, 52.1, 54.7, 56.0, 61.2, 66.8, 74.3, 80.5, 126.8, 127.9, 128.0, 128.3, 135.4, 136.0, 141.4, 147.2, 155.9, 160.1, 161.1, 162.7, 168.7, 170.8, 171.1; IR (film) 3302, 1721, 1659, 1596 cm^{-1}. This material was used without further purification.



Aminooxazoline-oxazole-thiazole-ethyl Ester 1.79. A solution of **1.78** (97 mg, 0.14 mmol) in 4 mL of EtOH/Et_3N (3:1) was hydrogenated over 100 mg Pd black at 100 psi. After 5 h, the reaction mixture was sonicated for 5 min and filtered through Celite. The solvents were concentrated, and the crude residue was chromatographed to give 65 mg (83%) of **1.79**: R_f = 0.33 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR ($CDCl_3$) δ 0.86-1.03 (m, 18H), 1.37 (t, J = 7.1 Hz, 3H), 1.48 (d, J = 6.2 Hz, 3H), 2.02-2.25 (m, 4H), 2.51-2.60 (m, 1H), 3.43 (d, J = 5.1 Hz, 1H), 4.19 (d, J = 7.7 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.76 (m, 1H), 5.05 (dd, J = 6.4 Hz and 9.1 Hz, 1H), 5.27 (dd, J = 7.1 Hz and 9.2 Hz, 1H), 7.14 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.3, 17.4, 18.0, 18.2, 18.8, 19.0, 19.7, 21.8, 32.0, 32.2, 32.9, 52.3, 55.3, 56.1, 61.4, 74.5, 80.3, 127.0, 135.6, 141.4, 147.3, 160.2, 161.3, 163.0, 171.2, 171.3, 171.6.

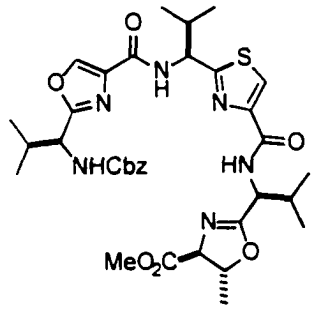


N-Cbz-oxazole-thiazole-ethyl Ester 1.80. Potassium carbonate (140 mg, 1.01 mmol) was added to a stirred solution of **1.75** (399 mg, 1.01 mmol) in 2 mL of CH_2Cl_2/H_2O (1:1). Benzyl chloroformate (0.17 mL, 1.21 mmol) was added via syringe, and the mixture stirred for 12 h at room temperature. The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and chromatographed (hexanes/EtOAc 5:3) to provide 454 mg (85%) of **1.80** as a white solid: mp 169.7-170.7 °C; R_f = 0.35 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ -34.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81-1.02 (m, 12H), 1.31 (t, *J* = 7.0 Hz, 3H), 2.10-2.20 (m, 1H), 2.49-2.56 (m, 1H), 4.33 (q, *J* = 6.9 Hz, 2H), 4.78 (app t, *J* = 7.1 Hz, 1H), 5.06 (m, 2H), 5.22 (t, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 8.8 Hz, 1H), 7.24-7.28 (m, 5H), 7.43 (d, *J* = 8.6 Hz, 1H), 8.00 (s, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.8, 13.6, 13.8, 14.1, 15.1, 28.1, 28.5, 50.2, 51.5, 56.8, 62.7, 122.4, 123.6, 124.0, 131.0, 131.5, 136.8, 142.9, 151.4, 155.6, 156.7, 158.9, 166.7; IR (neat) 3321, 3148, 3100, 1725 cm^{-1}.



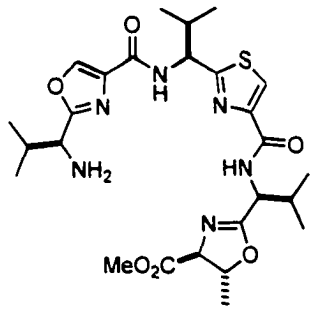
N-Cbz-oxazole-thiazole Carboxylic Acid 1.81. Lithium hydroxide monohydrate (28 mg, 0.67 mmol) was added to a stirred solution of **1.80** (155 mg, 0.29 mmol) in 3.7 mL of $MeOH/H_2O$ (4.5:1) at 0 °C and allowed to stir for 2 h with gradual warming to

room temperature, after which the previously cloudy solution had cleared. The solvents were concentrated, and the residue was partitioned between water and $CHCl_3$. The organic layer was discharged, and the aqueous layer was acidified and extracted with $CHCl_3$ (3 x 5 mL). The combined organic extracts were evaporated to give 145 mg (100%) of **1.81** that was used without further purification: ^1H NMR ($CDCl_3$) δ 0.75-1.05 (m, 12H), 2.09-2.21 (bs, 1H), 2.43-2.55 (bs, 1H), 4.78 (bs, 1H), 4.96-5.19 (m, 2H), 5.24 (bs, 1H), 5.59 (bs, 1H), 7.25 (bs, 5H), 7.59 (bs, 1H), 8.12 (bs, 1H), 8.15 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 13.7, 14.2, 15.0, 28.0, 28.4, 50.3, 51.6, 62.7, 123.7, 123.9, 130.7, 131.4, 137.3, 142.5, 151.5, 155.8, 159.2, 166.7; IR (neat) 3401, 3314, 3117, 2965, 1714 cm^{-1}.



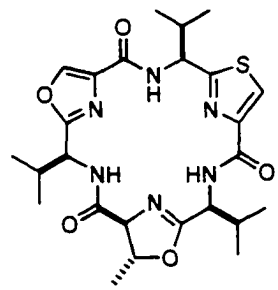
N-Cbz-oxazole-thiazole-oxazoline-methyl Ester 1.82. To amine **1.70** (75 mg, 0.35 mmol) and acid **1.81** (141 mg, 0.29 mmol) in DMF (4 mL) at -10 °C was added HOBt (126 mg, 0.93 mmol), and the mixture was stirred for 20 min. EDCI (73 mg, 0.38 mmol) was added, and stirring was continued for 10.5 h at room temperature. The reaction mixture was then diluted with EtOAc (8 mL), brine (4 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 8 mL). The organic phases were then washed successively with 10% citric acid (2 x 4 mL), saturated (aqueous) $NaHCO_3$ (2 x 4 mL), and brine (2 x 4 mL) and dried (Na_2SO_4). Flash chromatography of the residue (EtOAc/hexanes 5:4) provided 168 mg (83%) of

1.82 as a white foam that consisted of a mixture (approximately 1:1) of two rotomers: R_f = 0.06 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ -1.25 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80-0.99 (m, 18H), 1.33-1.37 (m, 3H), 2.12-2.23 (m, 1H), 2.41-2.50 (m, 2H), 3.69 (s, 3H), 4.20 (d, *J* = 6.9 Hz, 0.47H), 4.24 (d, *J* = 6.7 Hz, 0.52H), 4.72-4.85 (m, 3H), 5.00-5.11 (m, 2H), 5.26 (dd, *J* = 3.0 Hz and 6.3 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 0.48H), 5.48 (d, *J* = 9.1 Hz, 0.52H), 7.20-7.32 (m, 5H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 9.1 Hz, 0.48H), 7.73 (d, *J* = 9.3 Hz, 0.53H), 7.96 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 13.4, 13.5, 14.1, 14.2, 14.3, 14.8, 14.9, 16.3, 27.3, 28.0, 28.1, 28.4, 28.5, 47.8, 48.0, 50.3, 51.3, 62.7, 69.7, 69.8, 74.6, 118.7, 118.8, 123.5, 123.6, 123.8, 124.0, 131.0, 131.4, 136.9, 145.2, 151.4, 155.5, 156.0, 156.1, 158.9, 159.1, 163.4, 164.0, 166.1, 166.2, 166.6, 166.9; IR (neat) 3394, 3297, 2966, 1725 cm^{-1}. Anal. Calcd for $C_{34}H_{44}N_6O_8S$: C, 58.61; H, 6.36; N, 12.06. Found: C, 58.41; H, 6.44; N, 12.06.



Aminooxazole-thiazole-oxazoline-methyl Ester 1.77. A solution of **1.82** (101 mg, 0.15 mmol) in 3.3 mL of $EtOH/Et_3N$ (3:1) was hydrogenated over 100 mg Pd black at 100 psi. After 5 h, the reaction mixture was sonicated for 5 min and filtered through Celite. The solvents were concentrated, and the crude residue was chromatographed to give 57 mg (70%) of **1.77**: R_f = 0.45 (CH_2Cl_2/MeOH 90:10); ^1H NMR ($CDCl_3$) δ 0.86-1.00 (m, 18H), 1.38 (d, *J* = 6.3 Hz, 3H), 1.72 (bs, 2H), 2.06-2.23 (m, 2H), 2.44-2.48 (m, 1H), 3.72 (s, 3H), 3.80 (d, *J* = 6.0 Hz, 1H), 4.23 (d, *J* = 6.8 Hz, 1H), 4.72-4.87 (m, 2H),

5.26 (dd, J = 2.5 Hz and 6.6 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 13.4, 14.4, 14.4, 15.0, 16.4, 27.4, 28.5, 28.7, 47.9, 48.0, 51.3, 69.8, 74.9, 118.9, 130.7, 136.6, 145.1, 155.9, 156.1, 164.0, 166.3, 166.9; IR (neat) 3401, 3307, 2963, 1744, 1659 cm^{-1}. This material was taken directly to the next step.



Bistratamide D (1.4). Lithium hydroxide monohydrate (12 mg, 0.29 mmol) was added to a solution of **1.79** (80 mg, 0.14 mmol) in 3.4 mL of EtOH/H_2O (4:1) at 0 °C. After 3 h, the solution was neutralized with 1 M HCl, and then the solvents were evaporated to dryness by azeotropic distillation with toluene. The solid residue was dissolved in DMF (26 mL) and cooled to -10 °C, and diisopropylethylamine (0.05 mL, 0.31 mmol) and HATU (56 mg, 0.15 mmol) were added. The mixture was stirred at -10 °C for 2 h and then at room temperature for three days. After this time, the solvents were concentrated in vacuo, and the residue was partitioned between brine (25 mL) and EtOAc (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 13 mL). The combined organic extracts were washed successively with 10% aqueous citric acid (2 x 13 mL), saturated (aqueous) $NaHCO_3$ (2 x 13 mL), and brine (2 x 13 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 38 mg (48%) of **1.4** as a white solid, whose NMR data were in agreement with those reported:[18] R_f = 0.25 (EtOAc); $[\alpha]^{23}_D$ -29.8 (c 0.60, $CHCl_3$), lit[18] $[\alpha]^{23}_D$ -31 (c 0.33,

$CHCl_3$); λ_{max} = 230 nm, lit[18] λ_{max} = 232 nm; ^{1}H NMR ($CDCl_3$) δ 0.87-1.06 (m, 18H), 1.57 (d, *J* = 6.3 Hz, 3H), 2.18-2.25 (m, 1H), 2.34-2.43 (m, 2H), 4.09 (dd, *J* = 2.3 Hz and 9.1 Hz, 1H), 4.76 (m, 1H), 4.96 (m, 2H), 5.27 (dd, *J* = 5.2 Hz and 7.4 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 8.03 (d, *J* = 9.9 Hz, 1H), 8.10 (s, 1H), 8.15 (s, 1H), 8.62 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.6, 17.7, 18.1, 18.1, 19.0, 21.8, 31.1, 33.2, 34.4, 51.8, 53.0, 56.4, 74.0, 82.4, 123.6, 135.7, 140.9, 148.5, 159.1, 160.0, 163.2, 167.5, 169.3, 170.4; IR (neat) 3387, 2966, 16779, 1539 cm^{-1}.

IV. References

1 This work is reproduced, in part, from the following publication: Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *69*, 826-31.

2 a) Wipf, P. Synthesis and Structure-Activity Studies of Lissoclinum Peptide Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Vol. 12; Elsevier Science Ltd: New York, 1998; 187-228. b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115-34. c) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771-91.

3 Poncet, J. *Current Pharmaceutical Design* **1999**, *5*, 139-162.

4 Michael, J. P.; Pattenden, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1-23.

5 Moberg, C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 248-68.

6 a) Bertram, A.; Hannam, J. S.; Jolliffee, K. A.; González-López de Turiso, F.; Pattenden, G. *Synlett.* **1999**, 1723-6. b) Sokolenko, N.; Abbenante, G.; Scanlon, M. J.; Jones, A.; Gahan, L. R.; Hanson, G. R.; Fairle, D. P. *J. Am. Chem. Soc.* **1999**, *121*, 2303-4.

7 Wipf, P.; Fritch, P. C.; Geib, S. J.; Sefler, A. M. *J. Am. Chem. Soc.* **1998**, *120*, 4105-12.

8 Abbenante, G.; Fairle, D. P.; Gahar, L. R.; Hanson, G. R.; Pierens, G. K.; van den Brenk, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 10384-8.

9 Shioiri, T.; Hamada, Y.; Kato, S.; Shibata, M.; Kondo, Y.; Nakagawa, H.; Kohda, K. *Biochem. Pharmacol.* **1987**, *36*, 4181-5.

10 Ireland, C. M.; Roll, D. M.; Molinski, T. F.; McKee, T. C.; Zabriskie, T. M.; Swersey, J. C. Uniqueness of the Marine Chemical Environment: Categories of Marine Natural Products from Invertebrates. In *Biomedical Importance of Marine Organisms*; Fautin, D. G., Ed.; California Academy of Sciences: San Franscisco, 1988; 41-57.

11 Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477-80.

12 a) Schmidt, U.; Gleich, P. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 569-71. b) Schmidt, U.; Utz, R.; Gleich, P. *Tetrahedron Lett.* **1985**, *26*, 4367-70. c) Schmidt, U.; Griesser, H. *Tetrahedron Lett.* **1986**, *27*, 163-6.

13 Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223-6.

14 Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358-67.

15 a) Schmidt, U.; Weller, D. *Tetrahedron Lett.* **1986**, *27*, 3495-6. b) Kato, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2653-6. c) Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3251-4.

16 a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. b) Burgess, E. M.; Penton, H. R.; Taylor, E. A.; Williams, W. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI; 788.

17 Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975-7.

18 Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671-5.

19 Tavares, F.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2481-4.

20 Williams, D. R.; Lowder, P. D.; Gu, Y.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331-4.

21 Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907-10.

22 These conditions are a slight modification of those reported by Wipf in reference 17.

23 Aldrich Catalog Handbook of Fine Chemicals, 1996-1997.

24 Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235-49.

25 North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267.

26 Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

27 Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron Lett.* **1997**, *53*, 8323.

28 Villeneuve, G. B.; Chen, T. H. *Tetrahedron Lett.* **1997**, *38*, 6489.

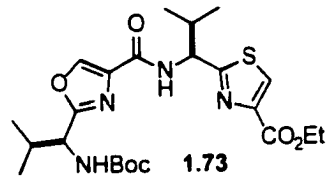
29 a) Meienhofer, J.; Kuromizu, K. *Tetrahedron Lett.* **1974**, *15*, 3259. b) Kuromizu, K.; Meienhofer, J. *J. Am. Chem. Soc.* **1974**, *96*, 4978.

30 The reader is referred to Schemes 1.1 and 1.5 of the introduction.

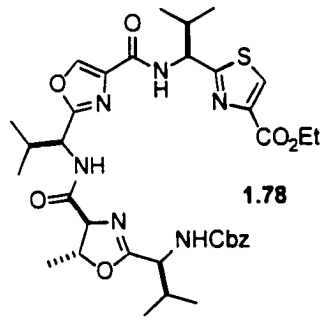
31 Copies of proton and carbon NMR spectra of the natural product were kindly provided by Professor Ireland.[18]

V. Spectra

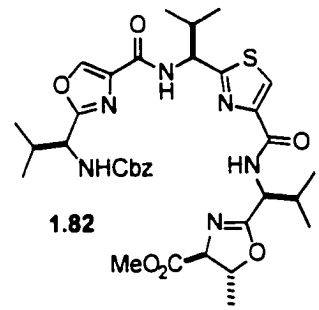
^{1}H and ^{13}C NMR spectra are included for the following compounds:



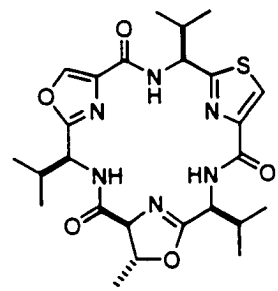
1.73



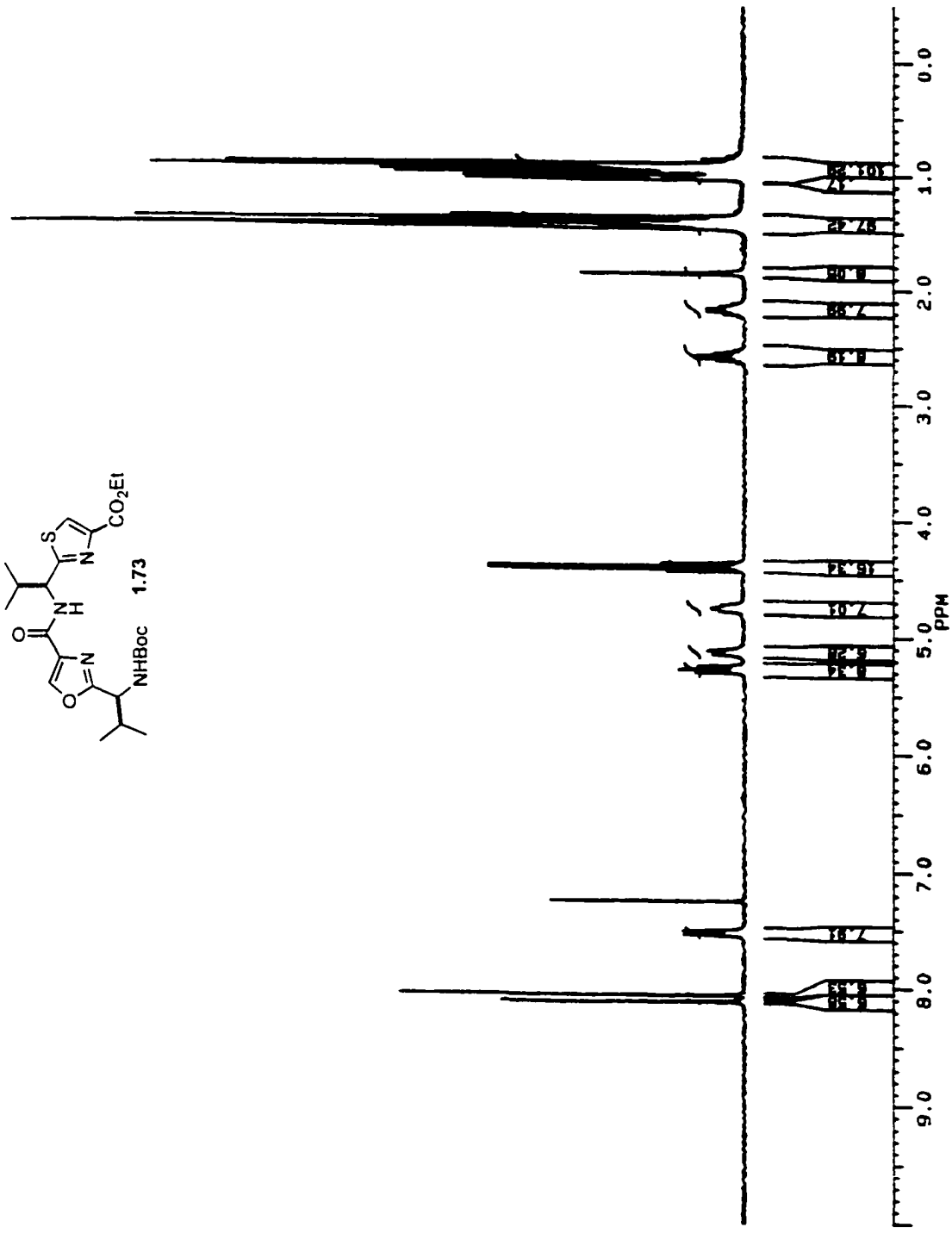
1.78

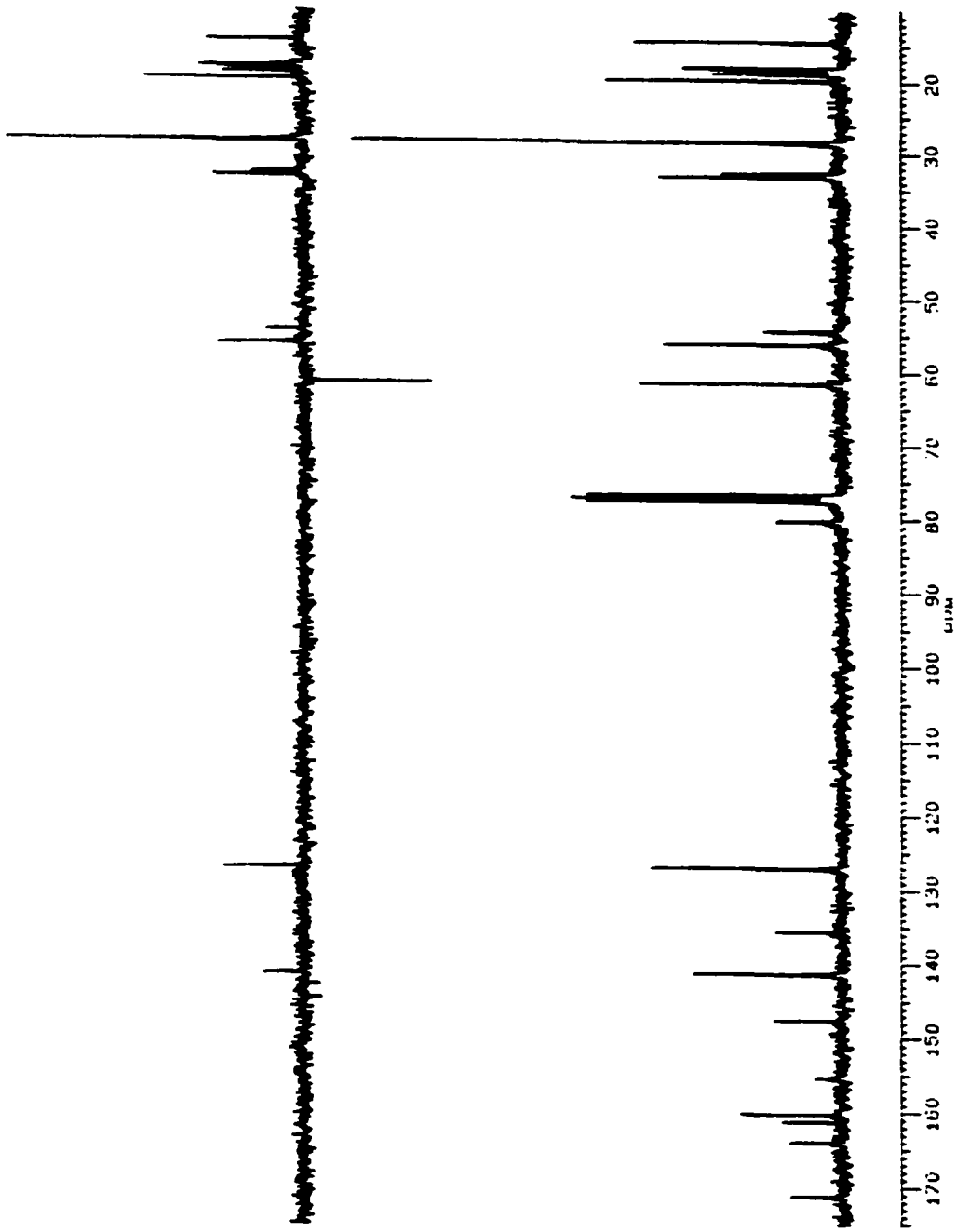


1.82

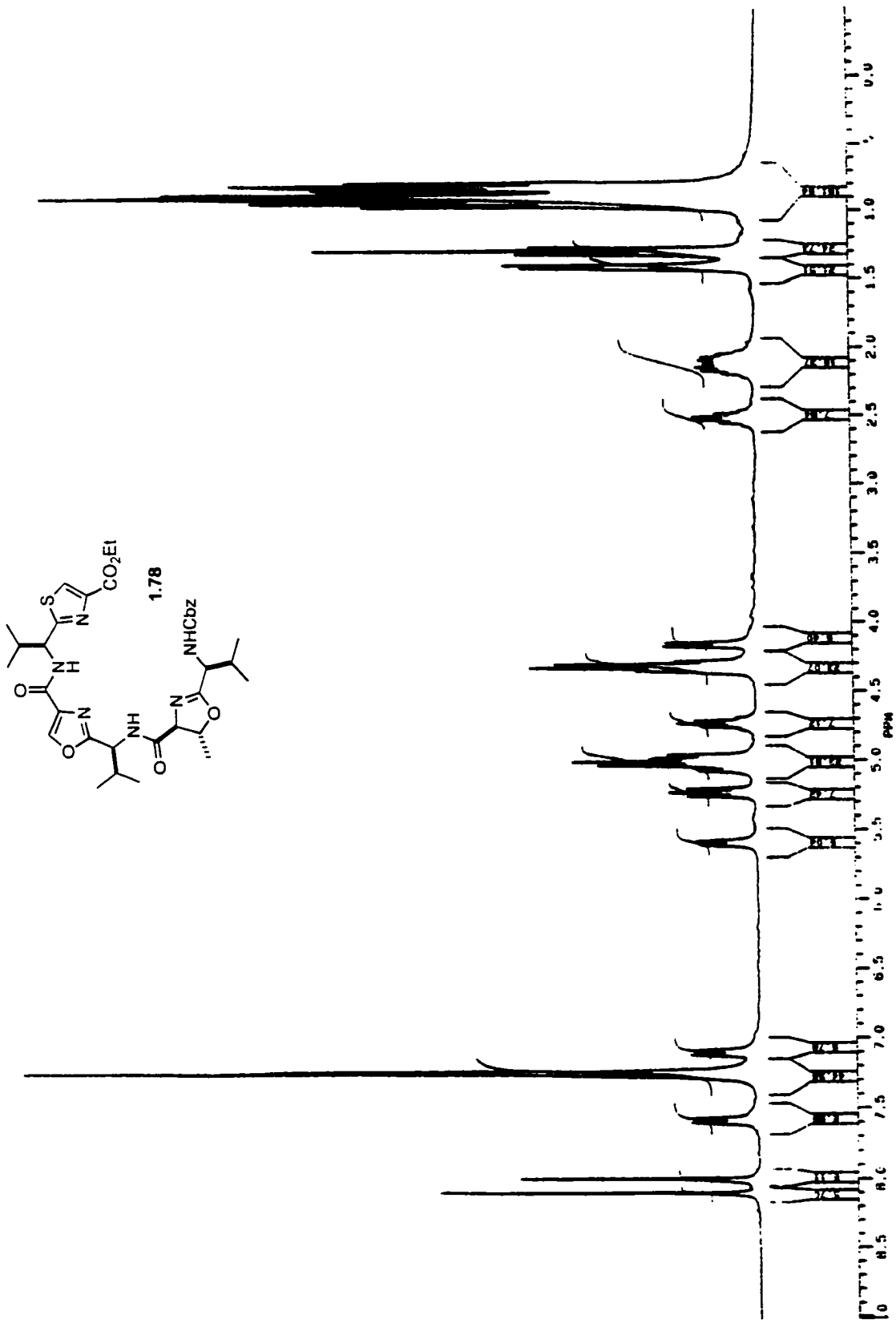


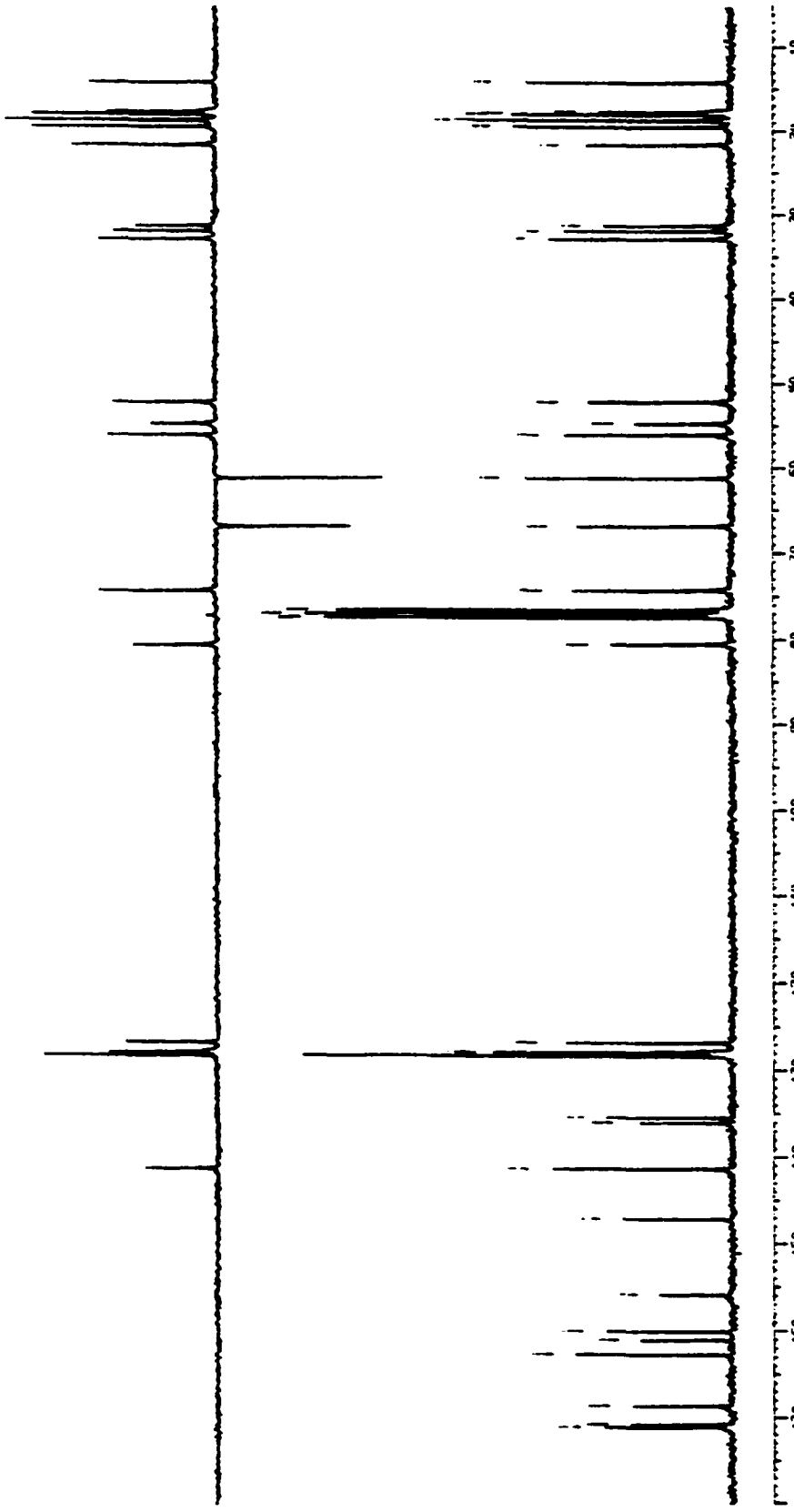
1.4



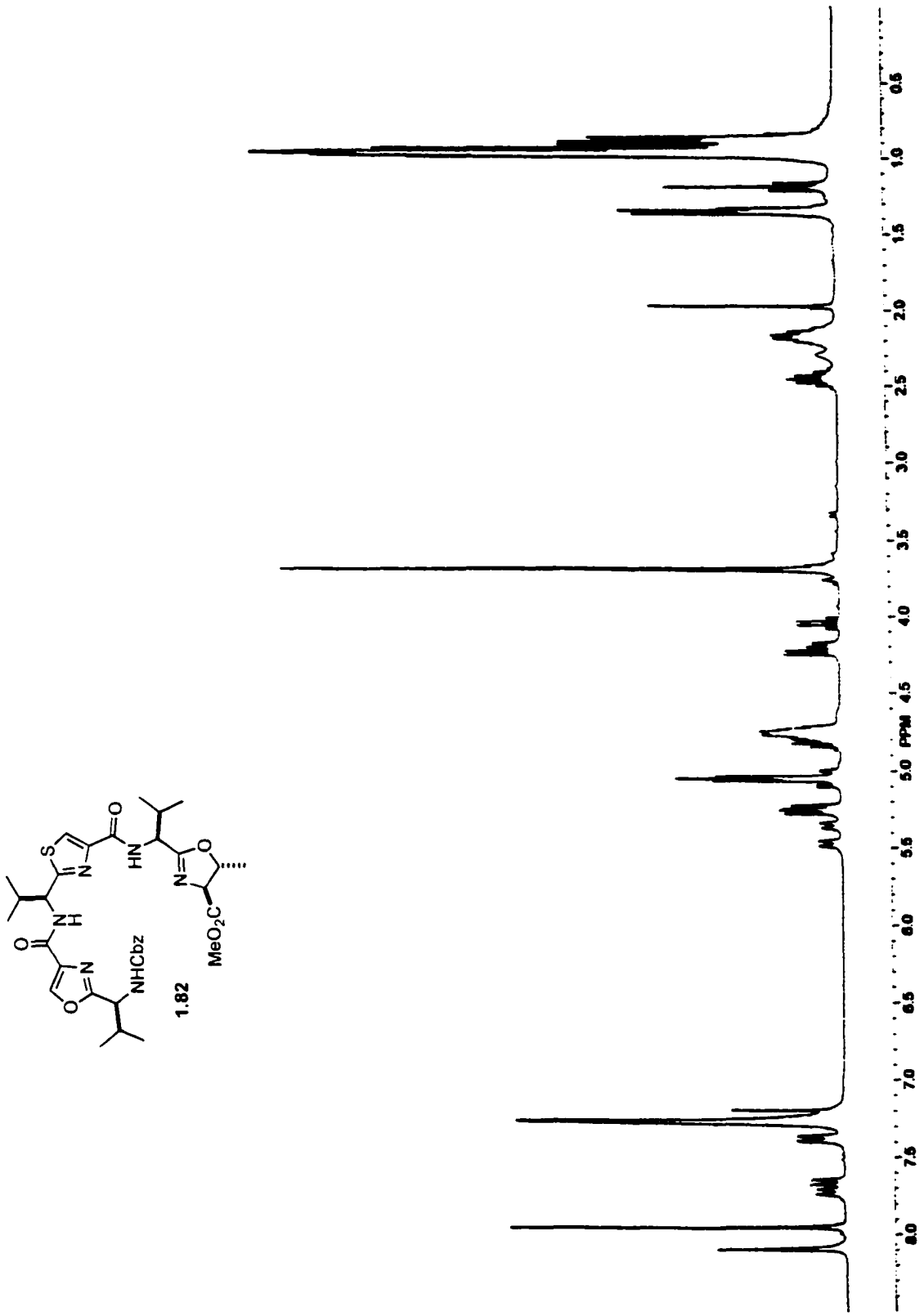


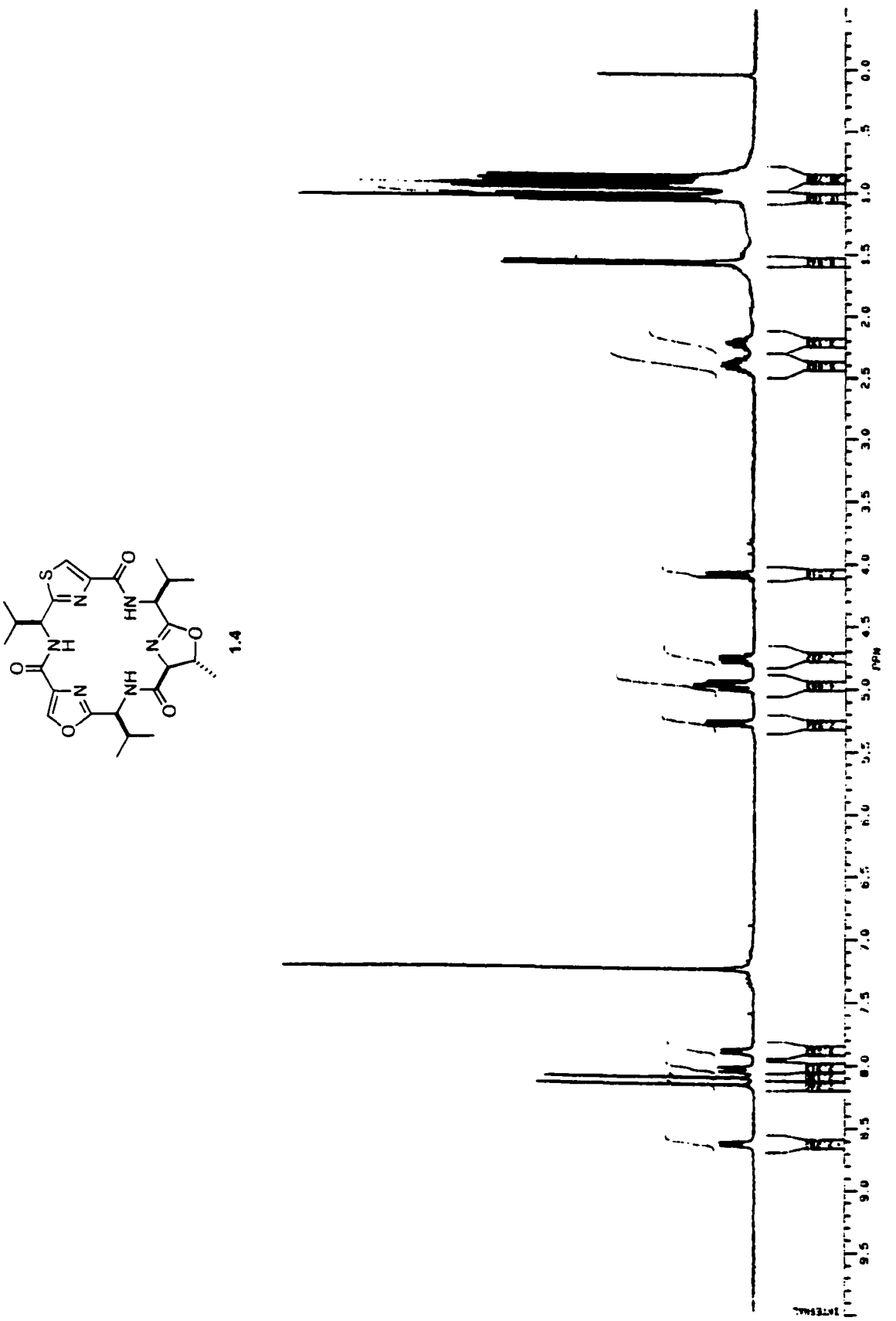
DEPT (top) and ^{13}C (bottom) NMR spectra for compound **1.73**

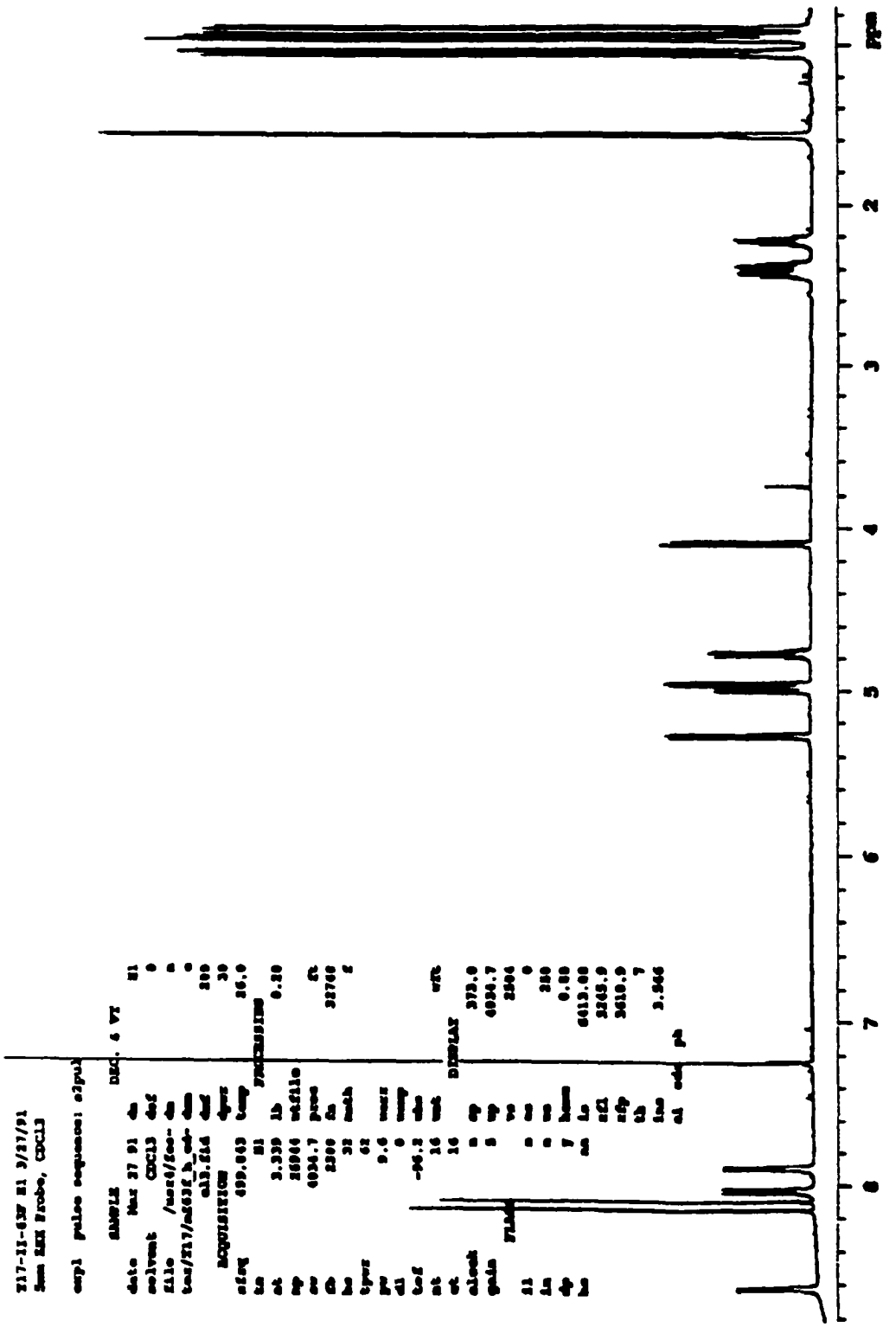




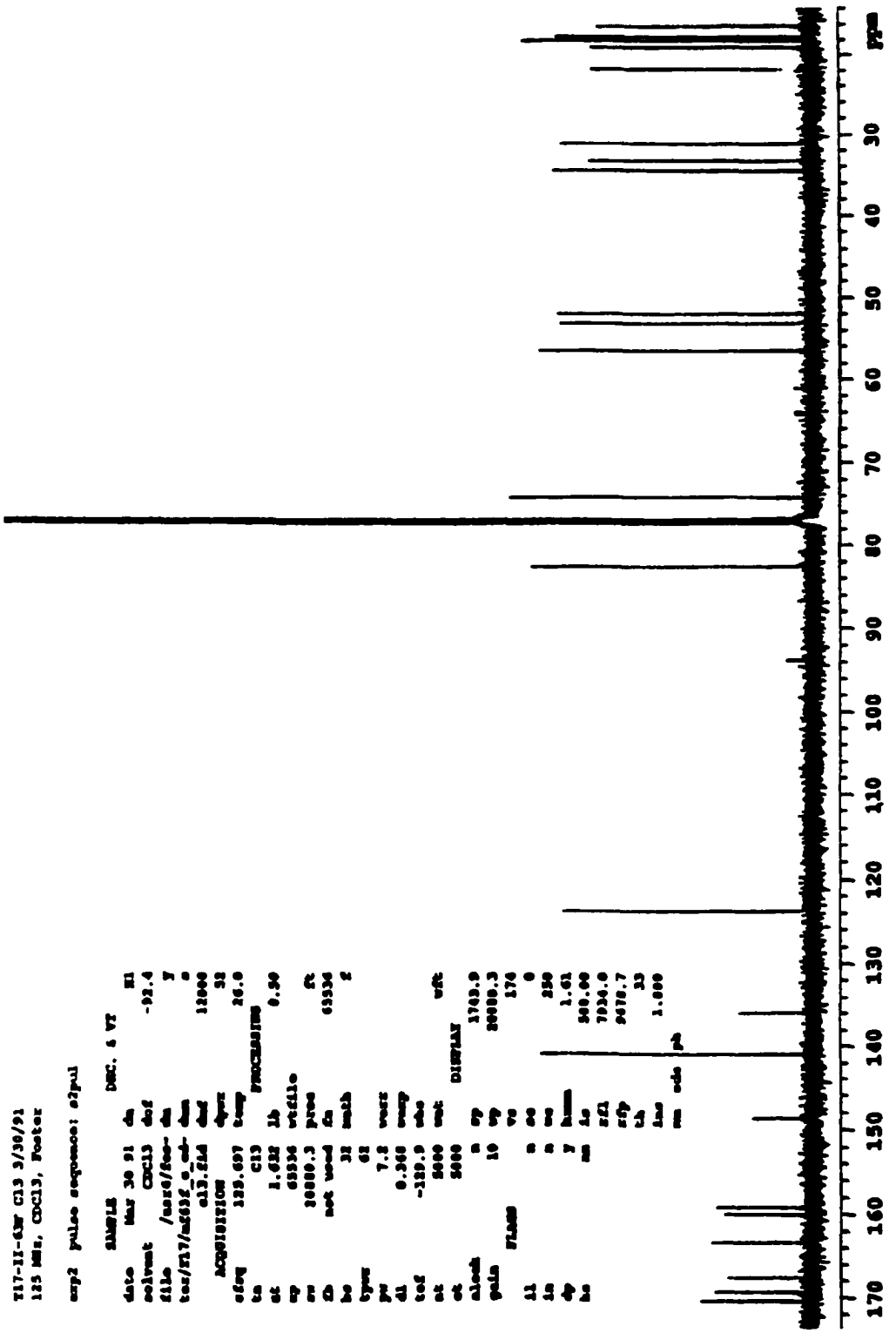
DEPT (top) and ^{13}C (bottom) NMR spectra for compound **1.78**







500 MHz ^{1}H spectrum of isolated Bistratamide D (**1.4**)[17]



125 MHz ^{13}C spectrum of isolated Bistratamide D (1.4)[17]

CHAPTER TWO

Investigations of Chiral Non-Racemic 5,7-Bicyclic Lactams

I. Introduction

A. Utility of 5,5- and 5,6-Bicyclic Lactams in the Construction of N*-Heterocycles*

For a number of years, the chiral, non-racemic, 5,5- and 5,6-bicyclic lactam systems have proven to be enormously useful templates for the synthesis of a variety of optically pure carbocyclic and heterocyclic natural and unnatural products.[1] A survey of some of the substituted pyrrolidines and piperidines accessible from the bicyclic lactam scaffold appears in Figure 2.1, and includes several products of pharmacological relevance. For example, Rolipram® is an antidepressant,[2a] indolizomycin possesses antibiotic properties,[2f] and azasugars, such as *rhammo*-1-deoxynojirimycin, possess anti-tumor and antibiotic activity.[1d] Some of the most attractive features of the here-to-fore described bicyclic lactam system include its ready accessibility from simple starting materials and the high degree of stereoinduction afforded in its subsequent manipulations, which lead to chiral products.

The general method for accessing the versatile chiral template **2.1** consists of the cyclodehydration of a γ- or δ-keto acid and a chiral amino alcohol simply by heating the two in toluene with azeotropic removal of water (Scheme 2.1).[1a] In this way, bicyclic

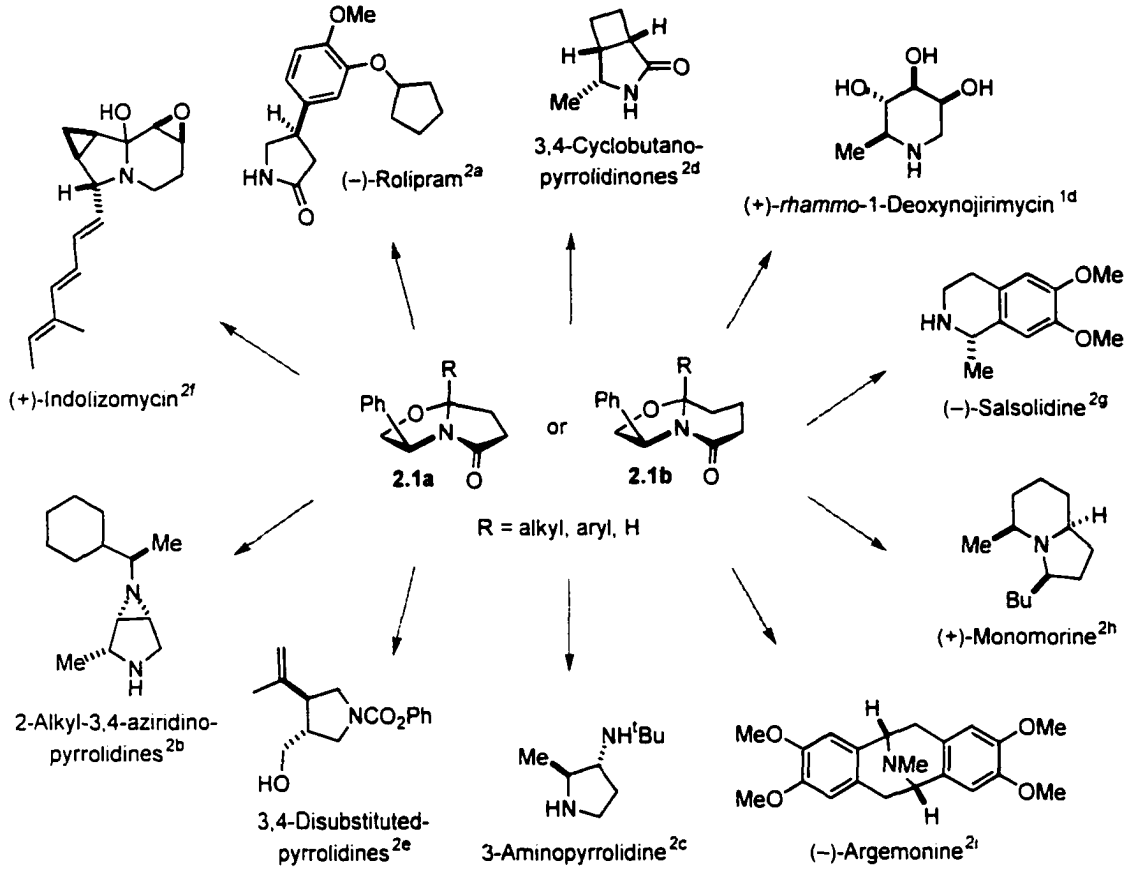
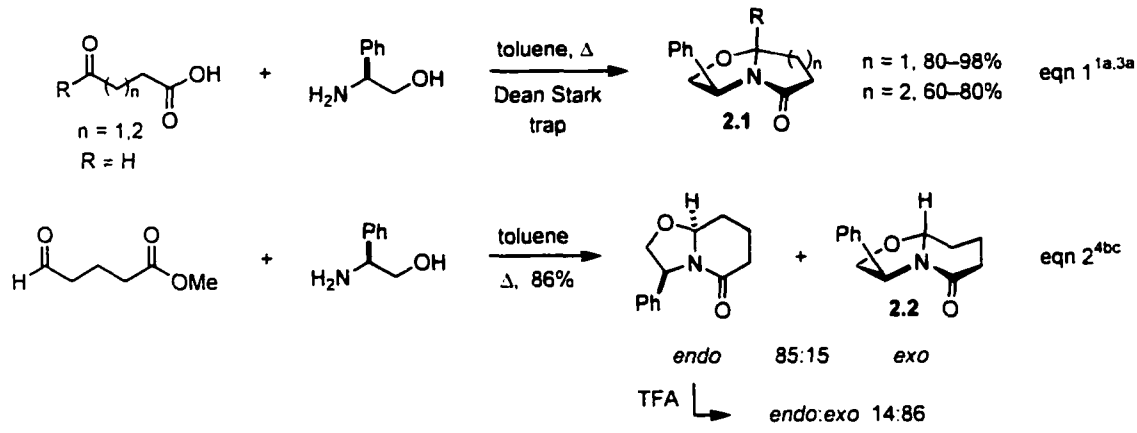


Figure 2.1. Bicyclic lactams provide access to a host of *N*-heterocycles

lactams **2.1**, with a variety of alkyl or aryl angular substituents, are readily obtained simply by utilizing the appropriately substituted keto acid (eqn 1).[3a] For the purpose of ultimately synthesizing *N*-heterocycles, (*S*)-phenylglycinol is commonly used as the chiral component. Thus, the 5,5-bicyclic lactams are obtained as single products in high yields while the 5,6-lactams are obtained as pure products after chromatographic purification of the mixture of diastereomers that is formed at the aminal center (approximately 4–10 to 1, favoring the *exo* angular substituent). Additionally, the angular hydrogen lactam **2.2** can be synthesized from the 4-formyl ester, methyl 5-oxopentanoate, using this method (eqn 2).[4bcd] In this case, the predominant isomer is the one with the *endo* angular hydrogen group, but isomerization with trifluoroacetic acid affords the *exo* product after chromatography.

Cyclodehydration Method:

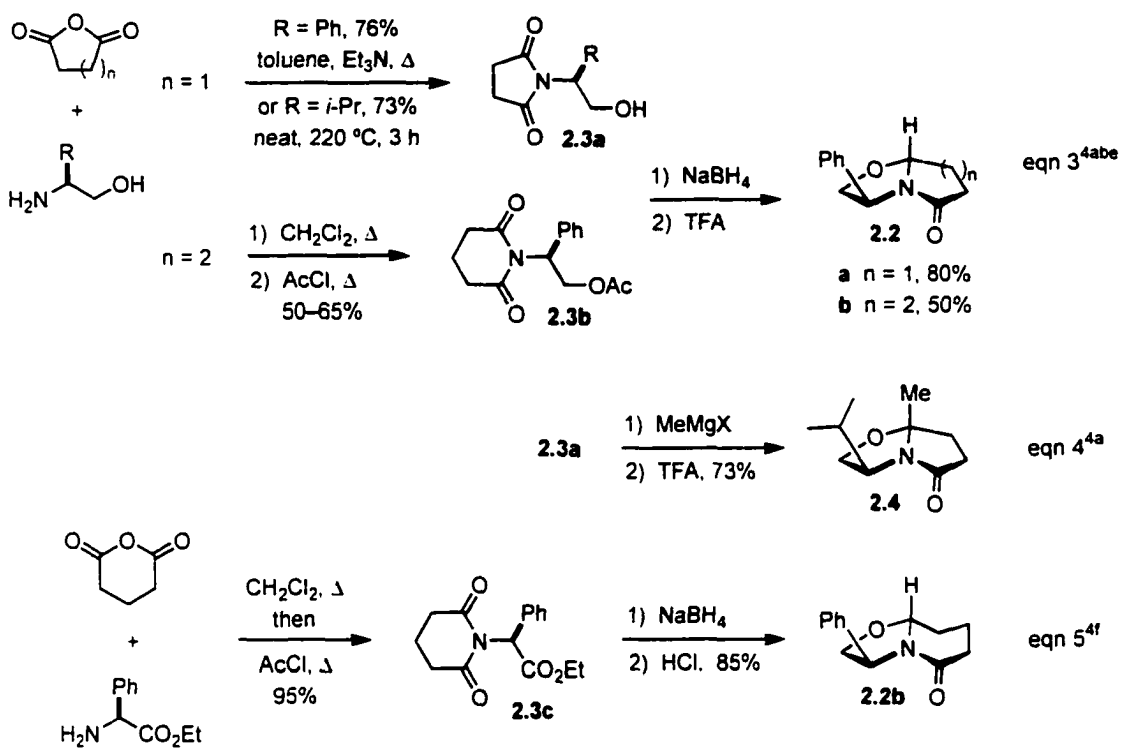


Scheme 2.1

Because formyl-containing carboxylic acids are frequently sensitive to the reaction conditions employed in the cyclodehydration method,[4a] a different synthesis of the angular hydrogen 5,5-bicyclic lactams was developed (Scheme 2.2).[4d] In this method,[4a] succinic anhydride (n=1) is heated with phenylglycinol and triethylamine in toluene at reflux, or with (*S*)-valinol as a neat mixture, to provide the *N*-substituted imide **2.3a** (eqn 3). Subsequent reduction of the imide to the hydroxy amide with sodium borohydride, followed by acid-catalyzed cyclization, provides the angular hydrogen lactam **2.2a** in high yield. Alternatively, addition of a Grignard reagent to imide **2.3a** provides still another route to angular "R" bicyclic lactams like **2.4** (eqn 4).

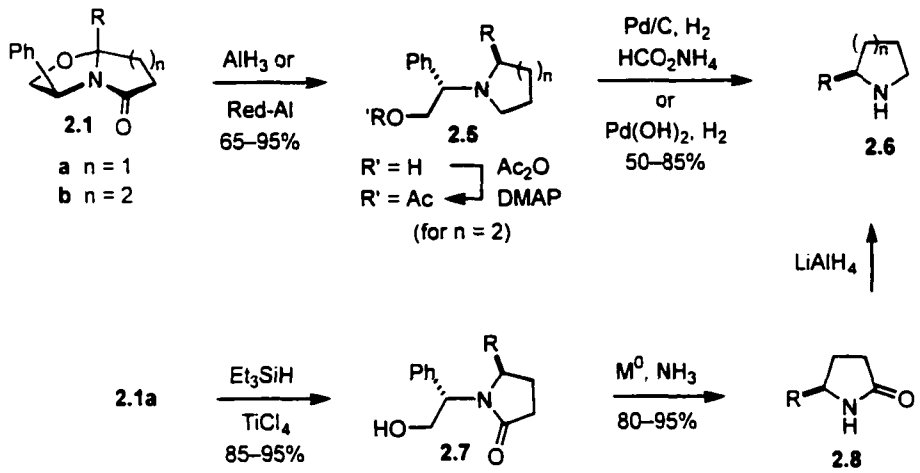
Closure to the imides derived from glutaric anhydride (eqn 3, n=2) are expedited when acetyl chloride is employed as a dehydrating reagent (Scheme 2.2).[4be] Hydride reduction of imide **2.3b** provides 5,6-lactam **2.2b** in 50% yield (eqn 3).[4bc] A more efficient route to this lactam uses ethyl phenylglycinate with glutaric anhydride to provide imide **2.3c**, in which the ester and the imide carbonyl are simultaneously reduced with sodium borohydride to produce lactam **2.2b** after treatment with acid (eqn 5).[4f]

Cyclic Imide Method:



Scheme 2.2

Concomitant reduction of the lactam carbonyl and the aminal center of bicyclic lactams **2.1** with alane or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) generates the *N*-substituted heterocycles **2.5** (Scheme 2.3), wherein reduction occurs predominantly with "retention" of the relative stereochemistry at the angular center (99:1 for n=1, 96:4 for n=2).[3acd] A single diasteromer is obtained after chromatographic purification of the crude mixture (n=1), or of the acetyl ester for the piperidine derivatives (n=2). Hydrogenation then affords enantiomerically pure 2-substituted pyrrolidines or piperidines **2.6** in good yields. Additionally, reduction of bicyclic lactam **2.1a** with triethylsilane and titanium tetrachloride furnishes *N*-substituted lactam **2.7** in good yields; again the relative stereochemistry of the angular center is



Scheme 2.3

maintained.[3c] Cleavage of the benzylic moiety in **2.7** under dissolving metal conditions produces 5-substituted piperidinones **2.8**.

Rationalization for the selectivity observed in hydride reductions of bicyclic lactams **2.1** has been presented. Complexation of the Lewis acidic aluminum reagent to the sterically less congested *endo* face of **2.1** weakens the angular C–O bond and promotes formation of the iminium ion species **A** (Figure 2.2). Hydride delivery from the aluminum, in an intramolecular sense, follows to provide the observed stereochemical result.[3acd] In a similar way, generation of the *N*-acyl iminium ion occurs readily in the presence of $TiCl_4$. The transition state structure **B** (Newman projection viewed down the exocyclic C–N bond) exhibits minimal 1,3-allylic strain by placing the smallest group, hydrogen, near the reactive carbon center. Also, the possibility for chelation involving the alkoxytitanium and the amide carbonyl may serve to favor this conformation. Hydride addition then occurs on the sterically more accessible α-face.[3c]

A variety of synthetic transformations performed on the bicyclic lactam core prior to hydride reduction allow one to synthesize more highly substituted *N*-heterocycles than those described in Scheme 2.3. Many such transformations begin from

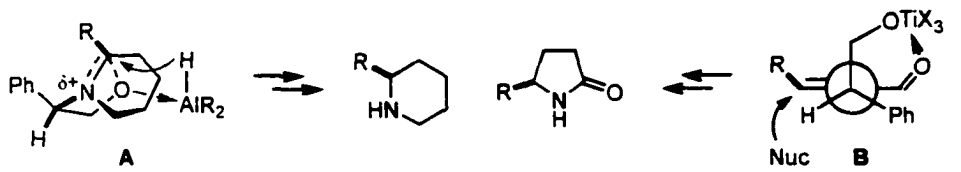
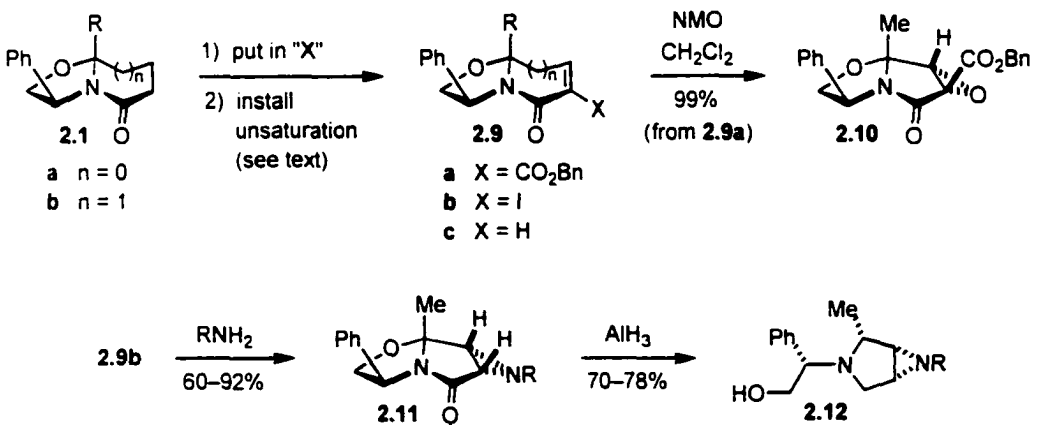


Figure 2.2. Origins of selectivity in hydride reductions of simple bicyclic lactams[3cd]

α,β-unsaturated lactam **2.9** (Scheme 2.4), which is easily obtained from lactam **2.1**. For example, oxidative elimination (with hydrogen peroxide) of an α-substituted-α-phenylselenide, obtained after a double deprotonation (lithium diisopropylamide) and "alkylation" (benzyl chloroformate, phenylselenyl bromide) sequence, provides unsaturated lactam **2.9a** in a straightforward fashion.[2a] The α-iodo species **2.9b** is obtained from **2.1** after the latter is diiodinated (1,2-diidoethane) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[5c] If the lactam is to remain unsubstituted (X=H), treatment of lactam **2.1** with potassium hydride and methyl phenylsulfinate in THF at reflux provides unsaturated lactam **2.9c** in 80–88% yield, and avoids the use of toxic selenium reagents.[6]

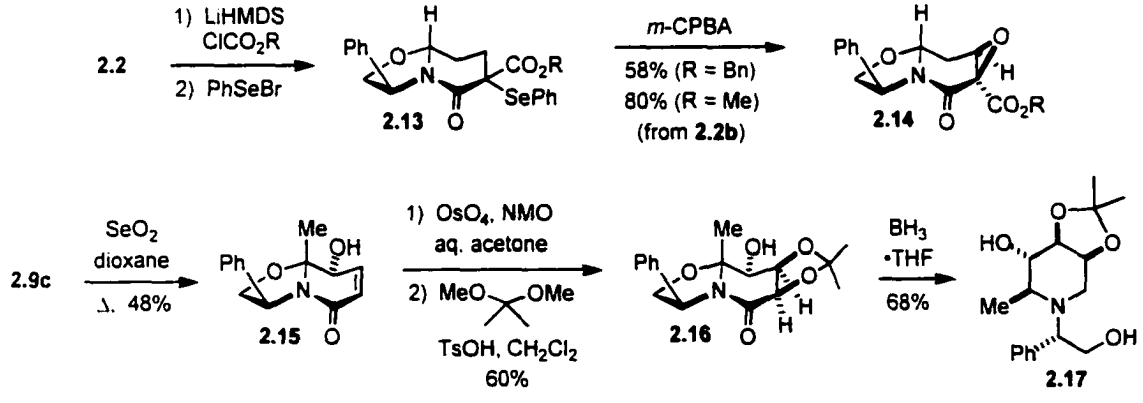
Subsequent treatment of unsaturated 5,5-bicyclic lactam **2.9a** with 4-methylmorpholine *N*-oxide in dichloromethane affords epoxide **2.10** in very high yield



Scheme 2.4

(Scheme 2.4).[5a] This sole product is the result of epoxidation from the *endo* face of the bicyclic system, where steric effects presented by the angular substituent are thought to prevent reaction from occurring on the *exo* face. Similarly, aziridination of unsaturated 5,5-lactam **2.9b** also occurs on the *endo* face to provide **2.11**.[2b] In several reactions of these lactams, including cyclopropanation[1a] and conjugate addition of organocuprates or of primary or secondary amines,[1c] addition occurs predominantly on the *endo* face when the angular substituent is methyl. Selectivity is reversed, however, for the angular hydrogen 5,5-lactams, giving rise to the *exo* products preferentially. Hydride reduction of aziridine **2.11** with alane proceeds with inversion of the relative stereochemistry at the angular center, providing the *syn*-trisubstituted pyrrolidine **2.12** in good yield.[1b] The "inverted" stereochemistry obtained in this transformation is a consequence of the fused 3-membered ring, which blocks access of the reducing agent to the concave face of the tricyclic system. This phenomenon is also observed in triethylsilane reductions of fused cyclobutane[1d] and pyrrolidine[1e] 5,5-lactams.

Oxygenation reactions of unsaturated 5,6-bicyclic lactams occur on the *exo* face, regardless of the angular substitution (Scheme 2.5). Epoxidation of angular hydrogen lactam **2.13** occurs subsequent to the oxidative elimination of the phenylselenide moiety



Scheme 2.5

with *m*-chloroperbenzoic acid (*m*-CPBA), to provide *exo* epoxide **2.14**.[5b] Dihydroxylation of lactam **2.15**, using NMO as oxidant with a catalytic amount of OsO_4, affords the diol, which is protected as the acetonide **2.16** by treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid.[1d] Reduction of both the lactam carbonyl and the angular center in **2.16** with borane provides the highly substituted piperidine **2.17**, possessing four contiguous stereocenters, in which the relative stereochemistry of the angular center is once again maintained (20:1). This is the expected result, since the *exo* face of lactam **2.16** is heavily encumbered. Hydrogenolysis of the benzyl group in **2.17** (not shown) completes this stereoselective synthetic route to the azasugar (+)-*rhammo*-1-deoxynojirimycin (Figure 2.1) which highlights the extreme versatility of the bicyclic lactam methodology in providing access to enantiomerically pure heterocyclic products.

B. Perhydroazepines as Interesting Synthetic Targets

Seven-membered nitrogen heterocycles are constituents of a plethora of compounds with interesting pharmacological properties. For example, all three constitutional isomers of benzazepine (1, 2, 3-) have antihypertensive activity, with several other properties, such as analgesic, antineoplastic, and antidepressant activity, varying depending upon the position of the nitrogen atom within the 7-membered ring.[7a] Specific examples are highlighted in Figure 2.3. Cephalotaxane is the parent structure of a group of compounds evaluated in clinical trials as antileukemia agents.[7b] Galanthamine, an *Amaryllidaceae* alkaloid, has analgesic properties,[7c] and clavicipitic acid is a member of the well-studied ergot alkaloids.[7d] Iminohomopiperidinium salts are selective inhibitors of inducible nitric oxide synthase (iNOS), and are therefore potential therapeutic agents for inflammatory conditions such as osteo arthritis and rheumatoid arthritis.[8] Balanol is known to be a potent inhibitor of the protein kinase C enzyme,

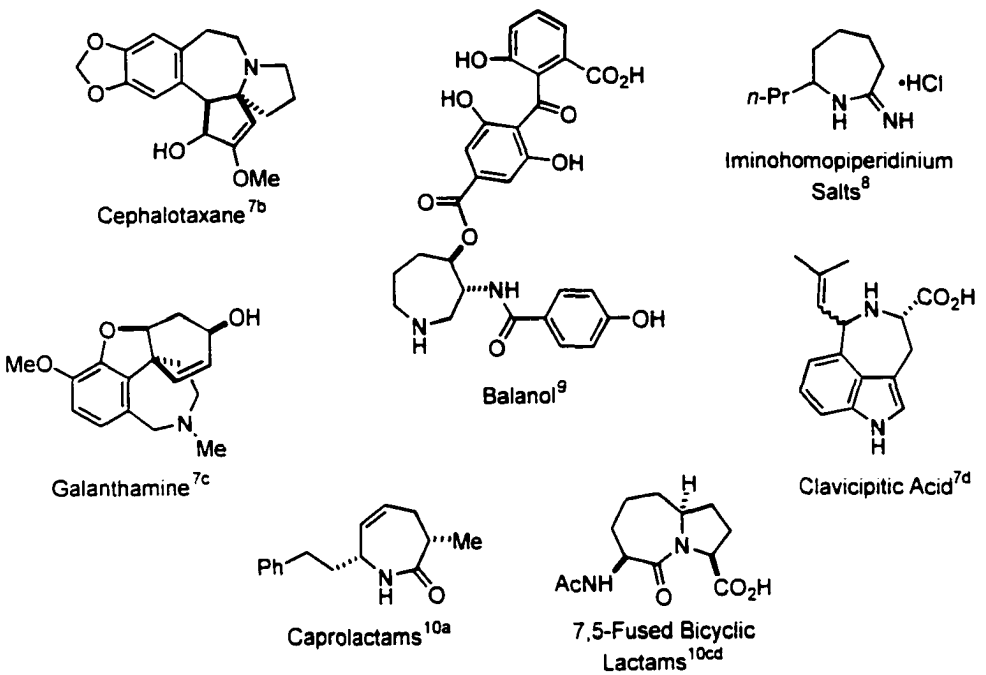
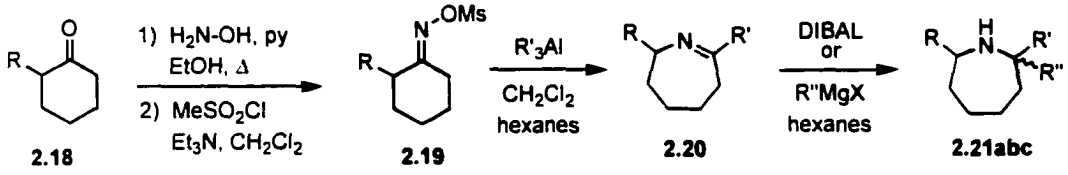


Figure 2.3. Perhydroazepines with Interesting Properties

which has been implicated in the progression of a wide variety of disorders of the central nervous and cardiovascular systems, and in diseases such as cancer and HIV infection.[9a] Additionally, substituted 7-membered lactams are studied as potential peptide turn mimetics,[10ab] and 7,5-fused bicyclic lactams are studied as conformationally restricted dipeptide surrogates.[10cd]

When considering simple 2-substituted perhydroazepines, general methods for their direct synthesis are few. One method, the trialkylaluminum-mediated Beckman rearrangement of cyclohexanone oxime sulfonates **2.19** (Scheme 2.6), provides access to the title compounds **2.21a** in good to moderate yields (47-70%) after reduction of the initially formed imine **2.20** with diisobutylaluminum hydride (DIBAL).[11] Since the regioselectivity follows the general rule for Beckman rearrangements, namely, preferential migration of the group anti to the oxime sulfonate, it is possible to obtain 2,7-disubstituted products **2.21b** from 2-substituted cyclohexanones. However, a



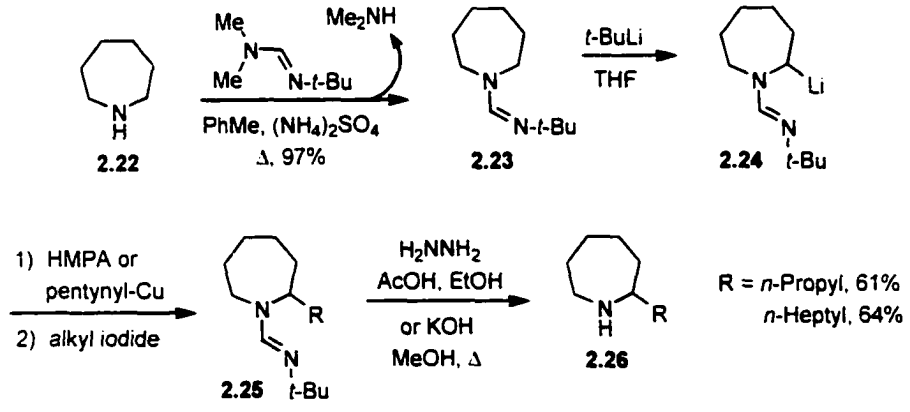
a R=R"=H; **b** R/R'=alkyl, R"=H; **c** R=H, R'=alkyl, R"=allylic/propargylic

Scheme 2.6

mixture of epimers at the newly formed tertiary center is obtained.[11a] Reaction of imine **2.20** with allylic or propargylic Grignard reagents allows for the synthesis of 2,2-disubstituted derivatives **2.21c**.[11b]

A different approach to these compounds involves alkylation of nitrogen-stabilized carbanions. Deprotonation of an sp^3-hydrogen α to the nitrogen can be both mild and efficient after placing an activating group on nitrogen that serves to deplete its' electron density.[12] Two such activating functionalities, which also enjoy ease of removal once their role is done, are the formamidine[13] moiety and the *tert*-butyloxycarbonyl[14] (BOC) group.

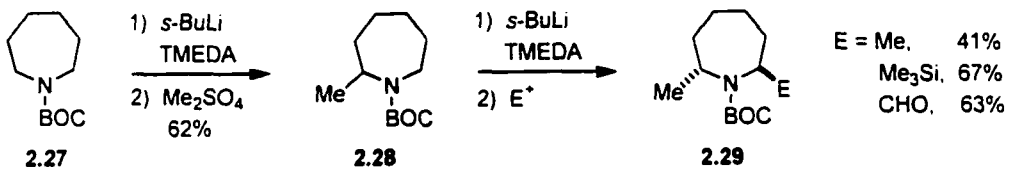
The *tert*-butylformamidine moiety is installed through amine exchange by heating dimethyl-*t*-butylformamidine and hexahydroazepine **2.22** with a catalytic amount of ammonium sulfate in toluene (Scheme 2.7).[13a] Metallation occurs smoothly with



Scheme 2.7

t-butyllithium in THF, and after addition of either HMPA, or pentynylcopper to generate the mixed cuprate, the metallated formamidines are readily alkylated to provide the 2-substituted compounds **2.25** in good yields. The formamidines are hydrolyzed by treatment with hydrazine and acetic acid or potassium hydroxide in alcohol solvent to provide the title compounds **2.26** in moderate yields.

Alternatively, the *N*-BOC perhydroazepine **2.27** is deprotonated with *sec*-butyl lithium/*N*,*N*,*N'N'*-tetramethylethylenediamine (TMEDA) in diethyl ether and alkylated with dimethyl sulfate to provide the mono-substituted compound **2.28** in moderate yield (Scheme 2.8).[14a] Repeating this sequence with a variety of electrophiles allows access to the *trans*-2,6-disubstituted derivatives **2.29**. Both preparation (BOC_2O) and removal (trifluoro-acetic acid, CH_2Cl_2) of the BOC group are facile under standard conditions.

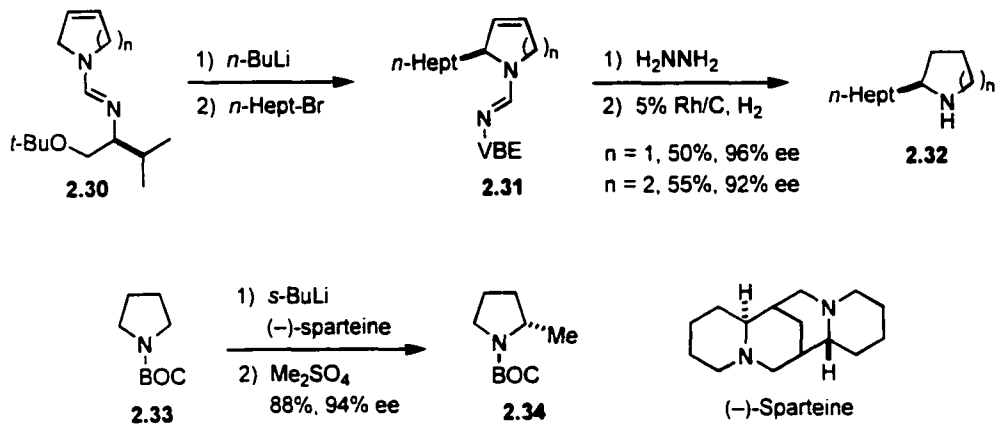


2.27 **2.28** **2.29**

Scheme 2.8

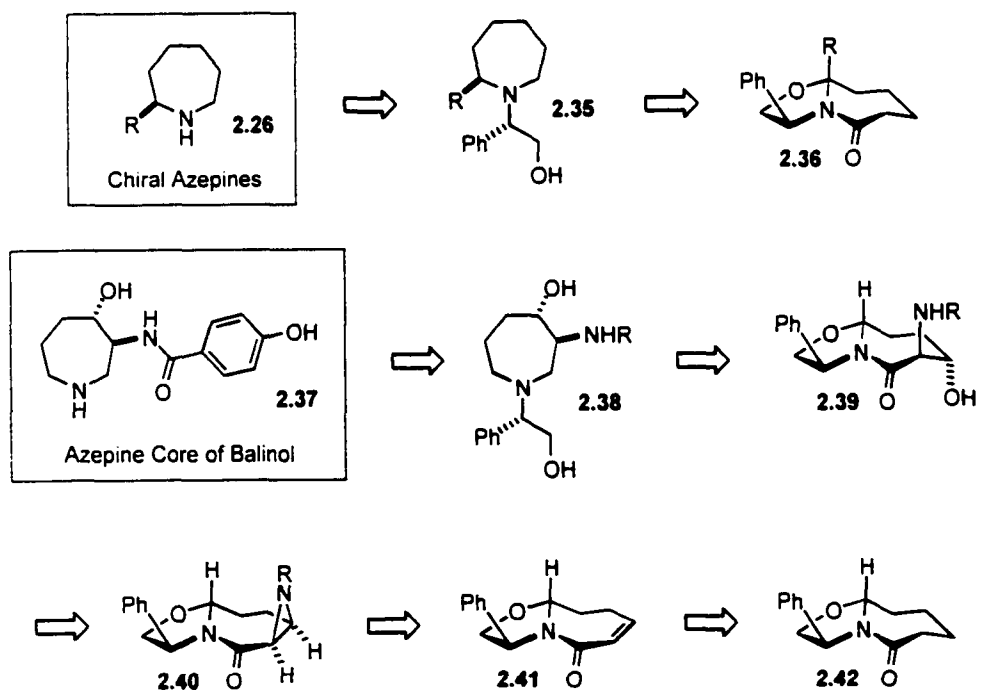
Advances in both the formamidine[13b] and the carbamate[14b] methodologies allow for the enantioselective syntheses of 2-substituted 5- and 6-membered *N*-heterocycles (Scheme 2.9). Asymmetric deprotonations of L-valinol-*tert*-butylether-derived formamidines **2.30** with *n*-butyllithium,[13b] or of *N*-BOC amines with *sec*-butyllithium and the chiral base (–)-sparteine,[14b] provide access to the chiral pyrrolidine[13b,14b] and piperidine[13b] derivatives, but neither method has been extended to the synthesis of chiral perhydroazepines.

In this regard, it was felt that development of the 5,7-bicyclic lactam scaffold **2.36**, in a manner similar to the existing 5,5- and 5,6-methodology, would serve to fill this gap



Scheme 2.9

by providing ready access to chiral 2-substituted azepines **2.26** (Scheme 2.10). Furthermore, an expedient approach to the azepine core **2.37** of balanol, which has been targeted in several formal syntheses of the natural product,[9b–h] should be realized from angular hydrogen lactam **2.42** by applying the chemistry described above.



Scheme 2.10

II. Results and Discussion

A. Synthesis of 5,7-Bicyclic Lactams

Following the conventional protocol for the synthesis of 5,5- and 5,6-bicyclic lactams,[1a] namely, heating of the keto acid (6-oxooctanoic acid[15a]) and amino alcohol in toluene with azeotropic removal of water for 1 day, served to provide a 2 to 1 mixture of (*R*)-phenylglycinol-derived 5,7-bicyclic lactam diastereomers **2.36** and **2.43** in very low yield (Table 2.1, entry b). After an extended reaction time of 5 days, the yield of the angular ethyl lactams was improved to 40% (entry c). A similar yield (38%) was obtained for the angular methyl lactams after 3 days (entry a), while the bulkier keto acid 6-oxo-8-methylnonanoic acid provided a 5 to 1 mixture of angular isobutyl lactams in very low yield (entry d).

In an effort to shift the poor ratios under equilibrating conditions, **2.44** and **2.45** were subjected to the original formation conditions. Heating of either one in wet toluene at reflux had no effect on the diastereomeric ratio. Since the products failed to equilibrate under the reaction conditions (Figure 2.4, step 3 is not reversible), the product ratio obtained from lactam synthesis most likely reflects the thermodynamic equilibrium position of the initially-formed disubstituted oxazolidine ring, which exhibits

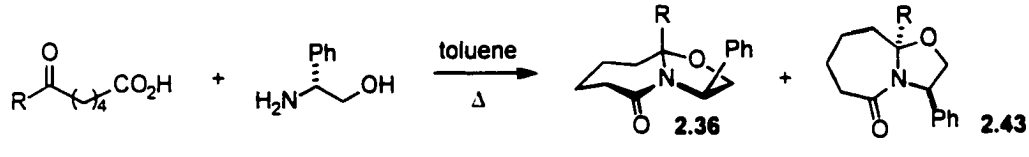


Table 2.1. Synthesis of (*R*)-Phenylglycinol Derived 5,7-Bicyclic Lactams

	R	Time	Yield	d.r.*
a	Me	3 d	38%	2.3 : 1
b	Et	1 d	11%	2.1 : 1
c	Et	5 d	40%	1.9 : 1
d	*i*-Bu	3 d	8%	5 : 1

* diastereomeric ratio

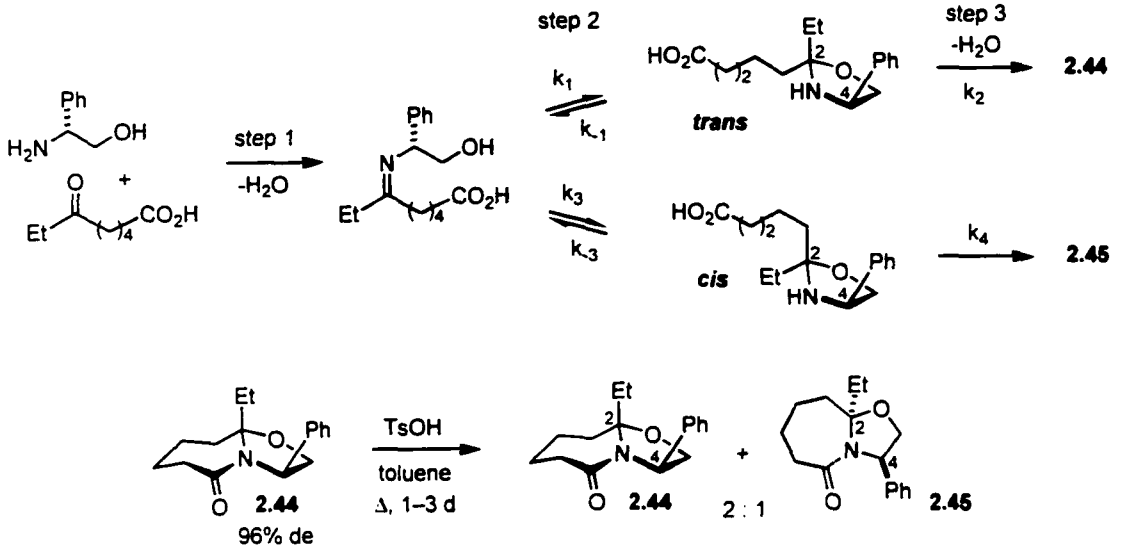
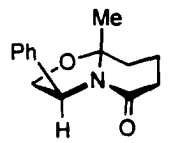


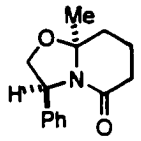
Figure 2.4. Equilibration of the bicyclic lactam with tosic acid

little preference for 2,4-*trans* versus 2,4-*cis* geometry.[4b] If closure of the 7-membered ring (*N*-acylation) were much faster (k_2»k_{-1}), then a more favorable ratio of products might be obtained if the *trans*-oxazolidine ring was formed preferentially as the kinetic product (k_1»k_3). Addition of p-TsOH to the wet toluene reaction quickly served to scramble the angular center of **2.44** from 96% to 33% de. After 3 days, the mixture remained 2:1 and reflects what is likely the thermodynamic mixture of lactam products.

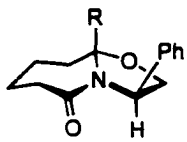
The major diastereomer of phenylglycinol-derived 5,7-bicyclic lactams **2.36** and **2.43** was tentatively assigned structure **2.36**, in which the angular R group resides on the *exo* face. This assignment was based on comparison with NMR data obtained for the 5,6-lactam diastereomers derived from 4-acetylbutyric acid and phenylglycinol (**2.46** and **2.47**), which is known to provide epimer **2.46** as the major product (Table 2.2).[3d] The signal for the benzylic proton in **2.46**, measured at 300 MHz in $CDCl_3$, appeared at 5.38 ppm while that for **2.47**, the minor 5,6-diastereomer, was found at 4.96 ppm. For each of the 5,7-lactams, the benzylic signal of the major lactam diastereomer was also found downfield from that for the minor epimer.



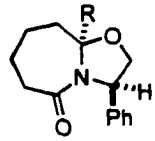
2.46 Major Diastereomer



2.47 Minor Diastereomer



2.36 Major Diastereomer



2.43 Minor Diastereomer

Table 2.2. ^{1}H NMR Shift of Benzylic Protons for Phenylglycinol Derived Bicyclic Lactams

Lactam	R	Diastereomer	^{1}H NMR shift
2.46		Major	5.38 ppm
2.47		Minor	4.96 ppm
2.48	Me	Major	5.33 ppm
2.49	Me	Minor	5.21 ppm
2.44	Et	Major	5.29 ppm
2.45	Et	Minor	5.19 ppm
2.50	*i*-Bu	Major	5.26 ppm
2.51	*i*-Bu	Minor	5.17 ppm

In hopes of making a firm stereochemical assignment, single frequency nuclear Overhauser effect (nOe) studies of angular methyl lactams **2.48** and **2.49** were undertaken.[16] Assignment of some of the ^{1}H NMR signals for compound **2.48** was as follows (Figure 2.5). The peaks located from 7.2–7.4 ppm were assigned to the protons on the phenyl ring, the peak at 5.3 ppm to the benzylic proton (H_a), those at 4.3 and 4.0 ppm to the other two oxazolidine protons (H_b and H_c, though it is not yet certain which is which), the multiplet from 2.6–2.5 ppm to the two protons adjacent to the lactam carbonyl, and the singlet at about 1.7 ppm to the protons of the angular methyl group. The integration of key signals upon irradiation of protons H_a, H_b, and H_c are summarized in Table 2.3. The largest interaction was observed between *geminal* protons H_b and H_c (3.7%), and it is the enhancement of the signal for the angular methyl group (H_{Me}) upon irradiation of these that became important for determining the absolute stereochemistry at the angular center. The moderate enhancement (1.2%) of the peak at 4.4 ppm upon irradiation of the benzylic proton (H_a) indicated that these protons were on the same

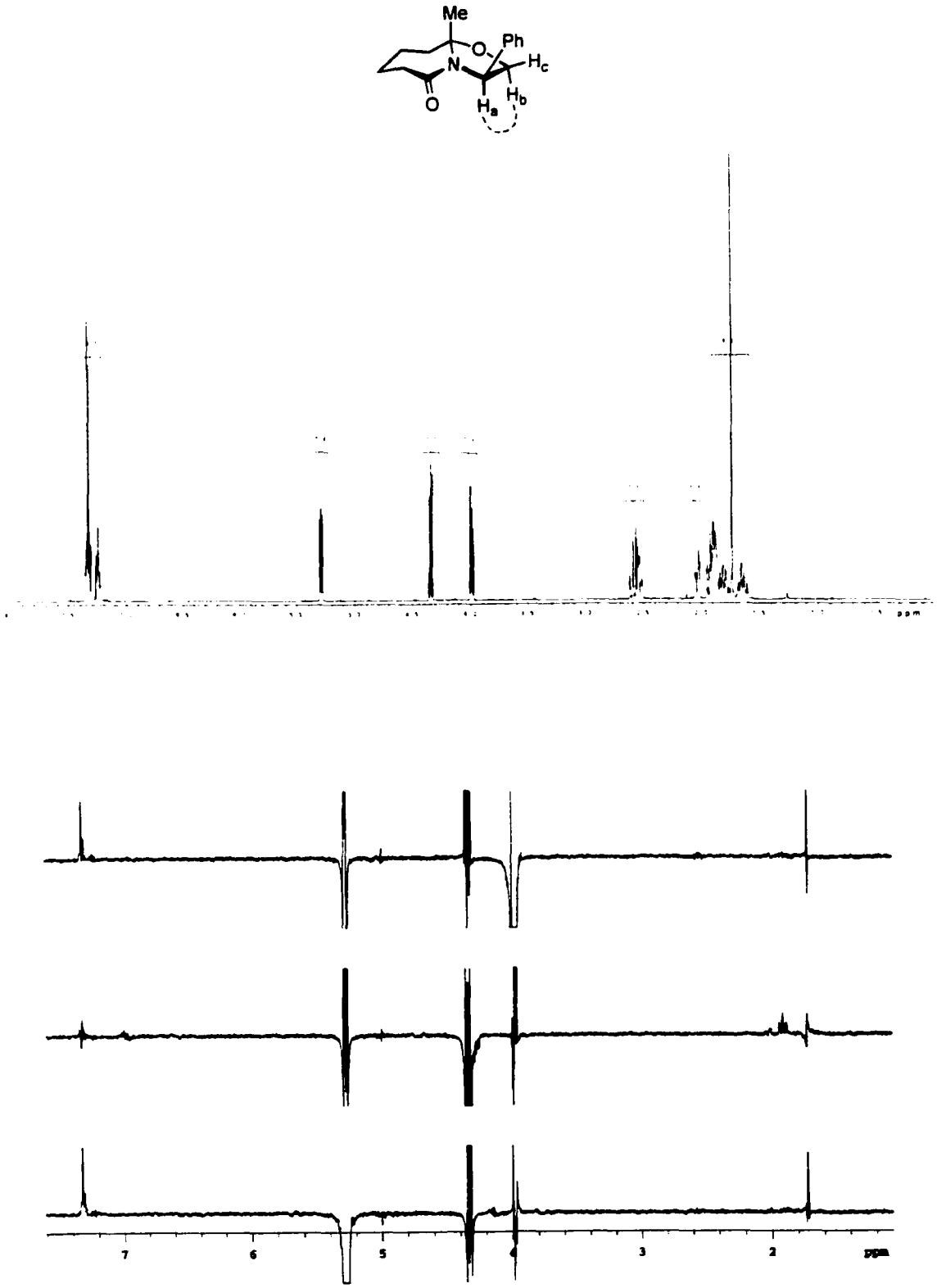


Figure 2.5. 500 MHz ^{1}H NMR spectrum (top) and nOe spectra (bottom) of **2.48**[16]

Table 2.3. Selected nOe Integration Data for Lactam **2.48**

Irradiated		Enhancement (%) of Signal at			
Proton	Signal	5.3 ppm	4.3 ppm	4.0 ppm	1.7 ppm
H_a	5.3 ppm	-	1.2	0.3	0.3
H_b	4.3 ppm	1.3	-	3.7	0.2
H_c	4.0 ppm	0.7	3.7	-	0.4

face of the oxazolidine ring. However, very little enhancement of H_{Me} was observed when any of H_a, H_b, or H_c were irradiated (<0.5%), and therefore no conclusion about the stereochemistry could be drawn from this experiment.

The 500 MHz ^1H and nOe spectra for lactam diastereomer **2.49** are shown in Figure 2.6, and selected integration data appear in Table 2.4. Again, a moderate interaction (1.1%) with H_a served to identify H_b. This time, moderate enhancement (1.0%) of H_{Me} was observed when H_b was irradiated, suggesting that the methyl group resided on the *endo* face of lactam **2.49**.

Table 2.4. Selected nOe Integration Data for Lactam **2.49**

Irradiated		Enhancement (%) of Signal at			
Proton	Signal	5.2 ppm	4.4 ppm	4.0 ppm	1.6 ppm
H_a	5.2 ppm	-	1.1	0.3	0.2
H_b	4.4 ppm	1.1	-	4.5	1.0
H_c	4.0 ppm	0.4	4.4	-	0.1

Finally, an X-ray crystal structure confirmed that the major lactam diastereomer **2.48** indeed possessed the *exo* angular methyl group (Figure 2.7).[17] Additionally, the 7-membered ring appeared to be in a half chair conformation, and the phenyl group of the chiral auxiliary resided somewhere between the pseudo equatorial and axial positions.

The structures of the angular ethyl lactams **2.44** and **2.45** were assigned based upon comparison of the ^1H NMR spectra to those for lactams **2.48** and **2.49**. Correlation by the shift of the benzylic peaks has already been discussed (p 73). Additionally, the aromatic protons and those adjacent to the carbonyl appeared similar between both major diastereomers and both minor diastereomers (Figure 2.8).

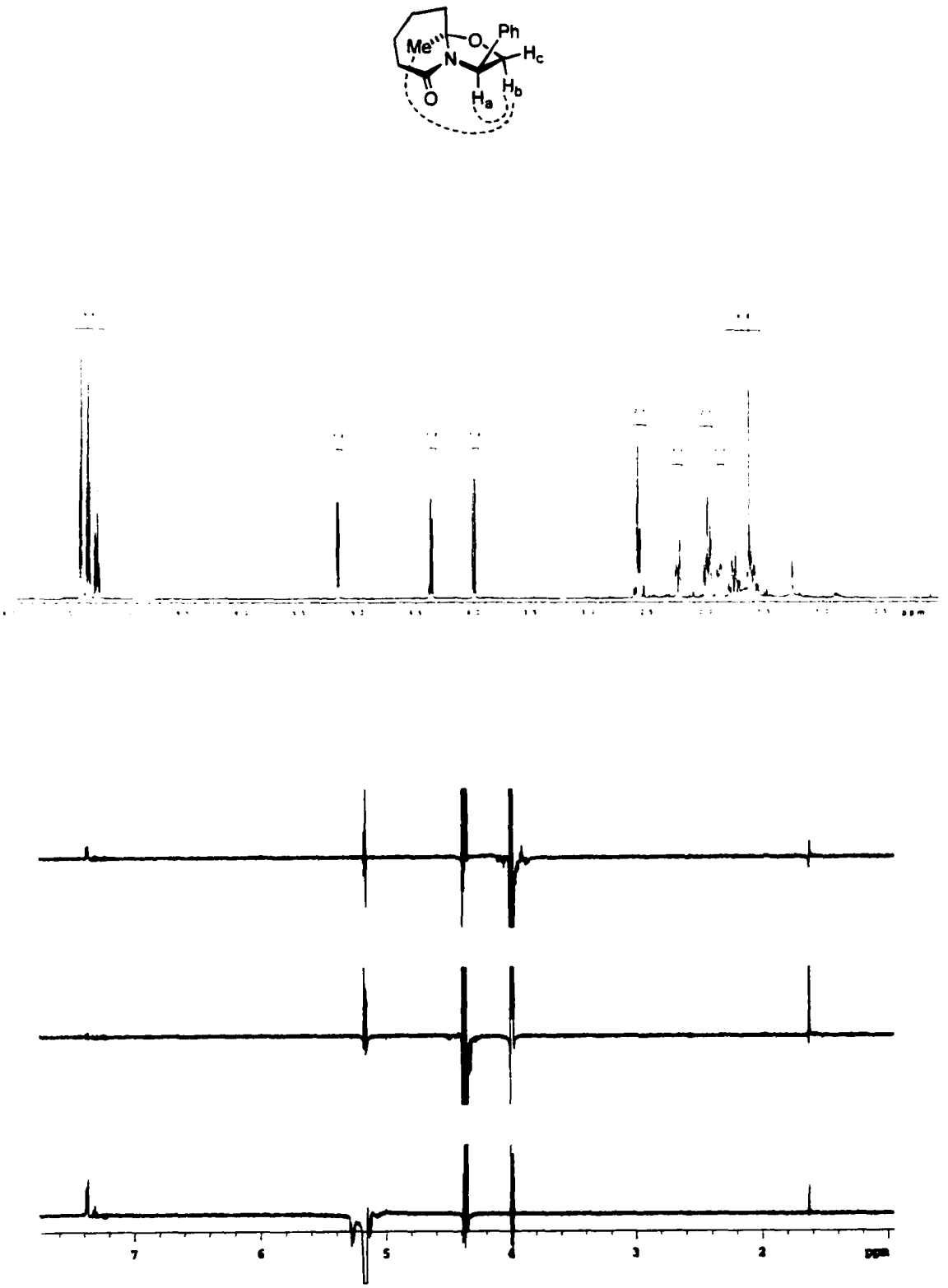


Figure 2.6. 500 MHz ^{1}H NMR spectrum (top) and nOe spectra (bottom) of **2.49**[16]

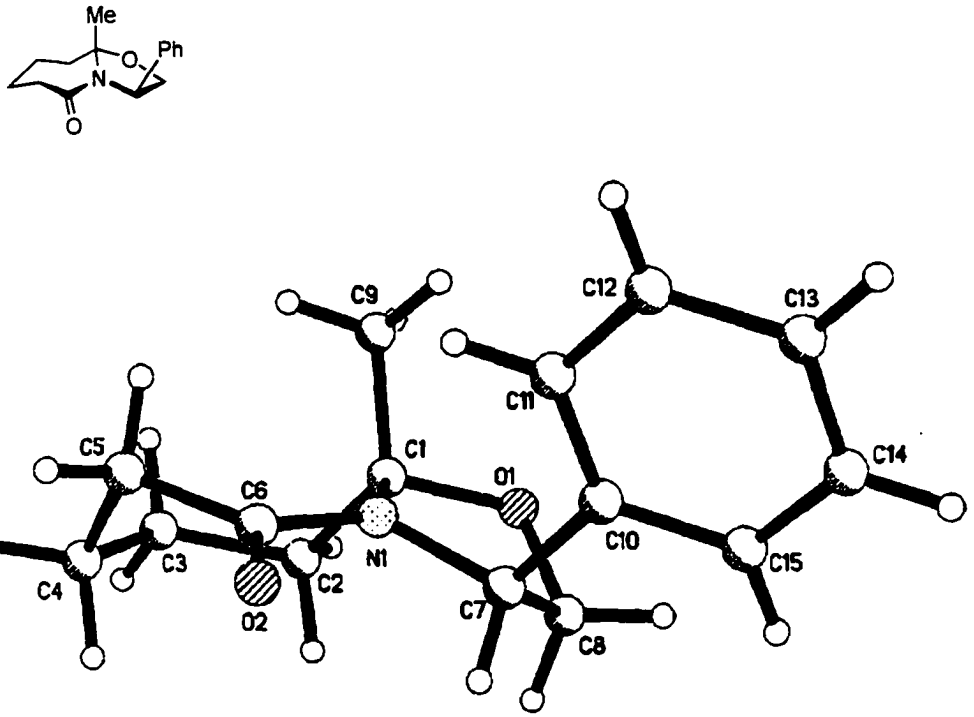


Figure 2.7. Single crystal X-ray structure of compound **2.48**[17]

B. The Search for an Improved Lactam Synthesis

Given that the isolated yield of the *exo* lactams **2.48** (methyl) and **2.44** (ethyl) was only about 25%, a significant amount of effort was directed toward finding means to improve both the yield, and the diastereoselection of bicyclic lactam formation. Since it had been shown that 5,5- and 5,6-bicyclic lactams could be synthesized from *N*-substituted cyclic imides,[4abef] early efforts focused on the synthesis of adipimide **2.52**, for which subsequent reaction with sodium borohydride or a Grignard reagent would provide access to 5,7-bicyclic lactams **2.36** with various angular substitution (Figure 2.9). Therefore, adipic anhydride[18] and phenylglycinol[4abe] or methyl phenylglycinate[4ef] were heated together in methylene chloride, toluene, or xylenes at reflux. However, adipimides **2.52** remained elusive despite use of all the reported tricks, including addition of triethylamine[4a] or acetyl chloride,[4bef] or both, or even heating them neat.[4a]

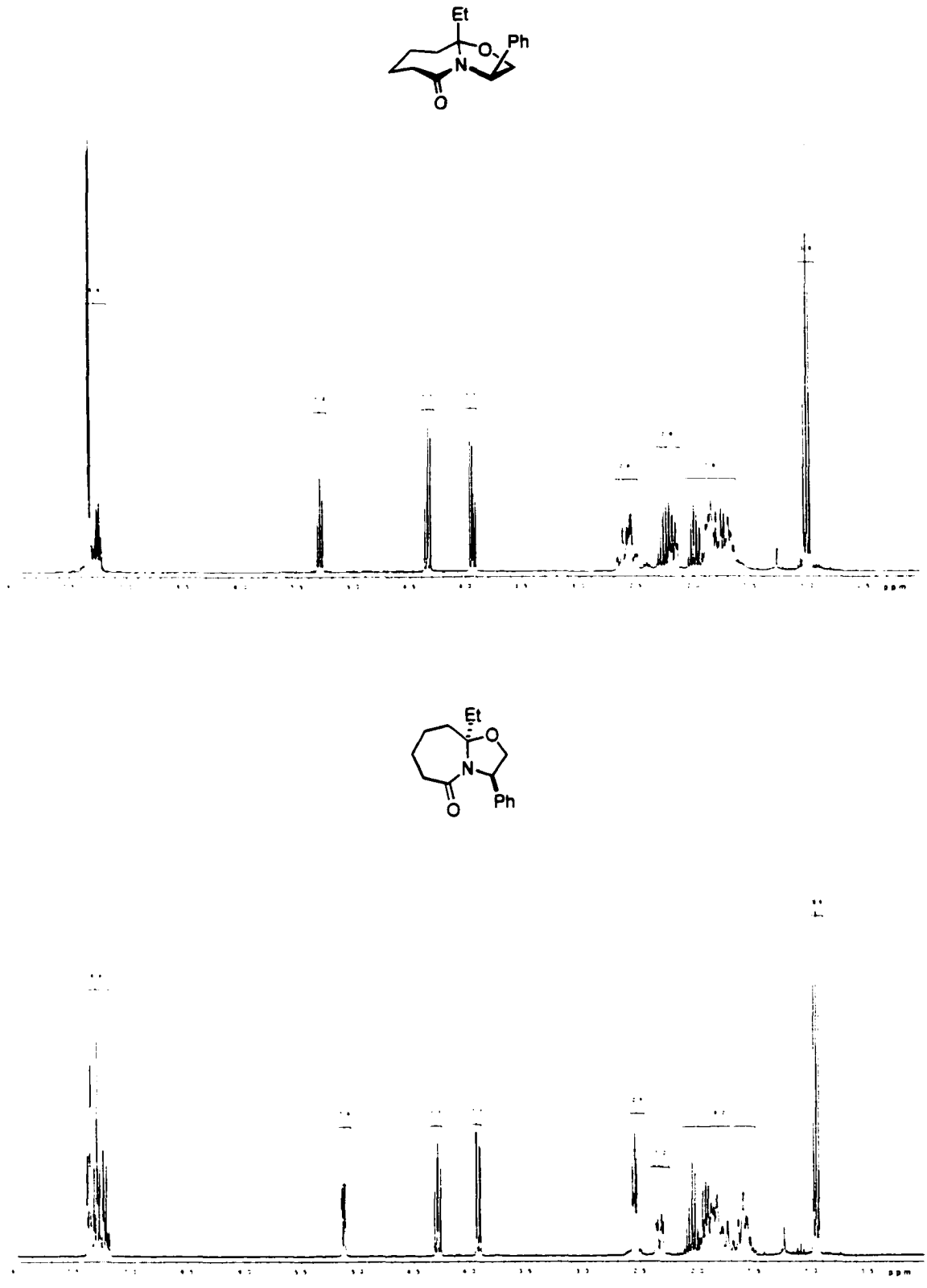


Figure 2.8. 300 MHz ^{1}H spectra for compounds **2.44** (top) and **2.45** (bottom)

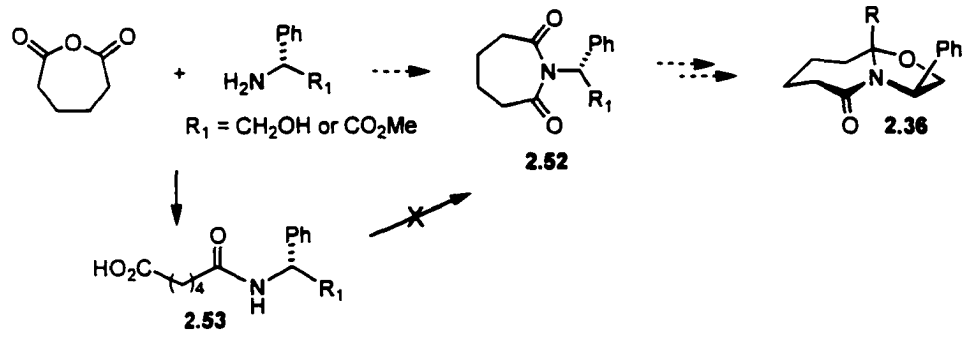


Figure 2.9. Proposed synthesis of the bicyclic lactam from an *N*-substituted adipimide

Either amine reacted readily with adipic anhydride to produce amide **2.53**, however cyclization to the 7-membered *N*-heterocycle **2.52** upon prolonged heating or further treatment with acetyl chloride or thionyl chloride (to make the acid chloride, which was thought to be a better leaving group in acyl displacements) was not observed.

The phenylglycinol-derived angular hydrogen 5,6-bicyclic lactam **2.2** has been synthesized by the cyclodehydration method using the formyl ester methyl 5-oxopentanoate, followed by acid-catalyzed epimerization of the angular center (Scheme 2.1, p 62).[4bc] Since the analogous 5,7-lactam **2.42** was of interest for the pursuit of balanol, methyl 6-oxohexanoate[19] was heated to reflux with phenylglycinol in toluene (Figure 2.10). After two days, no trace of **2.42** was observed, however, after one day, the ^{1}H NMR spectrum of the crude reaction mixture indicated that closure of the 5-membered oxazolidine ring, producing **2.54** (R=H), had occurred.[20] Interestingly, the

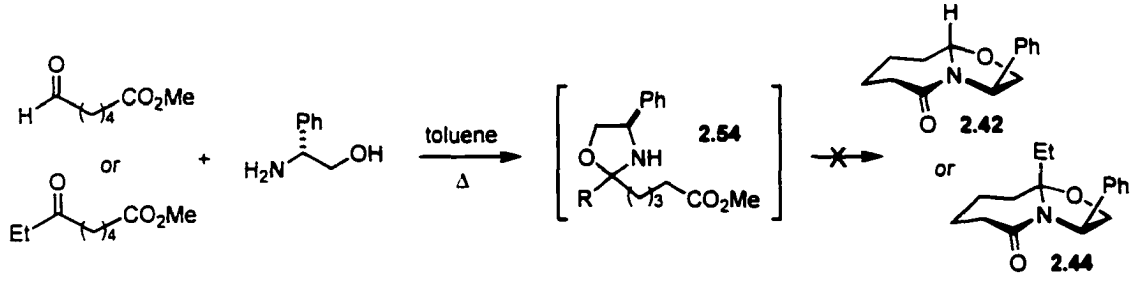


Figure 2.10. Attempted lactam synthesis from formyl and keto methyl esters

use of methyl 6-oxooctanoate in this reaction failed to provide angular ethyl lactam **2.44**. It is not clear why the change from an acid to an ester would so dramatically change the outcome of this process.

The construction of bicyclic lactams with three other chiral amino alcohols, (*S*)-valinol,[21ab] (*S*)-*tert*-leucinol,[21c] and (*S*)-*geminal*-dimethylphenylglycinol,[21d] was investigated with the anticipation that varying the bulk of the amino alcohol R group might serve to produce a higher ratio of lactams **2.55** to **2.56** (Table 2.5). Even though only one valinol-derived lactam diastereomer was isolated, reactions using these chiral auxiliaries to produce the angular ethyl lactam were unfortunately much lower yielding than that employing phenylglycinol. In fact, no bicyclic lactam derived from *tert*-leucinol was obtained with either 6-oxooctanoic acid or 6-oxoheptanoic acid, implying that these systems are sensitive to steric bulk to the point that they do not form at all.

Having exhausted the reported methods for 5,5- and 5,6-lactam synthesis without improving matters, it was decided to explore new approaches. In the standard method for bicyclic lactam synthesis, the double cyclodehydration of an amino alcohol and keto acid becomes a favorable process as water, one of the reaction products, is azeotropically removed from the mixture through the use of a Dean Stark trap. Might LeChatlier's principle be favorably utilized through the use of another solvent that forms

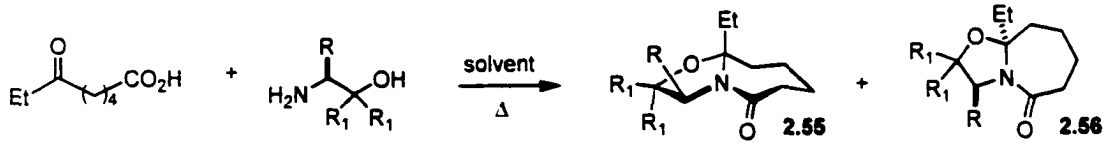


Table 2.5. Use of Various Amino Alcohols in Conjunction with 6-Oxooctanoic Acid

Lactam	R	R_1	Solvent	Time	Yield	**2.55** : **2.56**
2.57	*i*-Pr	H	xylenes	6 d	6%	one product
2.58	*t*-Bu	H	toluene	3 d	decomposed*	
2.59	Ph	Me	xylenes	6 d	6%	2.5 : 1

* The same result was observed when 6-oxoheptanoic acid was used.

an azeotrope with water? Aside from this property, the solvent in question should also be immiscible with and less dense than water, such that the traditional method could still be used.

Aside from toluene, solvents meeting these requirements include ethyl acetate, benzene, *n*-heptane, and xylenes (Table 2.6). It was hoped that a lower reaction temperature would improve the product diastereoselection, however, after 6 days in benzene at reflux (entry d) lactams **2.44** and **2.45** were obtained in a 1.8 to 1 ratio in only 18% combined yield. Use of *n*-heptane provided a similar result (entry e), while use of ethyl acetate led to no reaction at all (entry c). It was thought that the chemical yield of **2.44** and **2.45** might be increased by using xylenes, whose azeotrope contains twice the amount of water as does the azeotrope with toluene. After 6 days in xylenes at reflux, lactams **2.44/2.45** were obtained in 40% yield, as a 2.3 to 1 mixture (entry h).

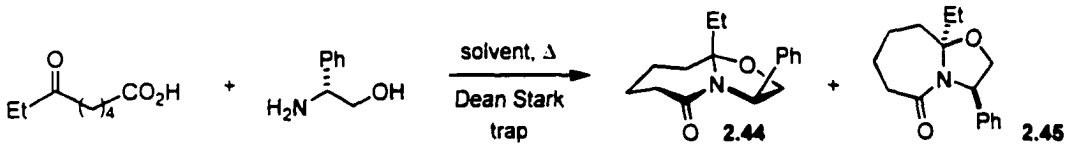


Table 2.6. Examination of Different Solvents in the Bicyclic Lactam Synthesis

			Azeotrope[a]				
	Solvent	bp[a] °C	% H_2O	bp °C	Time	Yield	**2.44** : **2.45**
a	MeOH	64.7			1 d	No Reaction	
b	DME	85			2 d	No Reaction	
c	EtOAc	77.2	8.5	70.4	1 d	No Reaction	
d	benzene	80.1	8.9	69.3	6 d	18%	1.8 : 1
e	*n*-heptane	98.4	12.9	79.2	5 d	22%	2.1 : 1
f	toluene	110.7	13.5	84.1	5 d	40%	1.9 : 1
g	MeCN	80.1	16.3	76.5	1 d	No Reaction	
h	xylenes	137–144	35.8[b]	92[b]	6 d	40%	2.3 : 1
i	xylenes	137–144	no Dean Stark trap		8 d	27%	2.7 : 1
j	1-butanol	117.4	42.5	92.7	1 d	No Reaction	
k	2,6-lutidine	144.0	51.8	96.0	2 d	Decomposed	

a Data from CRC or Aldrich.[22] b Data is for *meta* isomer.

This result is not significantly different from the one obtained in toluene (entry f). Perhaps interesting is the fact that this reaction proceeds, albeit in lower yield, in xylenes at reflux in the absence of water removal (entry i).

Since it seemed unclear what solvent feature was desirable for this reaction, for example, whether it was the polarity,[23] boiling point, or the percentage of water in the azeotrope, a variety of other solvents were examined (Table 2.6). Acetonitrile (entry g), 1-butanol (entry j), and 2,6-lutidine (entry k) all form azeotropes with water and were effective at dissolving the reactants, but none of these proved effective for the desired transformation. No reaction was observed with methanol (entry a) or dimethoxyethane (entry b), either. It appears as though lactam formation only occurs in the relatively nonpolar solvents, in which the amino group may be less well-solvated, and hence more reactive toward the ketone carbonyl.

The results from the experiments employing the keto or formyl esters indicate that the 5-membered oxazolidine ring is formed readily, and suggest that the difficult step in bicyclic lactam synthesis is ring closure at the amide bond. A variety of additives have been reported to aid in amide bond formation[25] and were examined in the context of the desired transformation (Table 2.7). In the case of the formyl ester (entries a,b), isolation of any lactam product would be an improvement. Alas, none of the metal ions summarized in entry a provided lactam **2.42**.[25a] With the strong Lewis acids $BF_3 \cdot OEt_2$ and $TiCl_4$, oxazolidine formation was noted by crude ^1H NMR,[20] but the reaction did not progress to afford lactam **2.42** (entry b). Dibutyltin oxide has been used as an esterification catalyst in the synthesis of unsaturated ω-lactams from primary amino acids.[25bc] However, with 6-oxooctanoic acid, inclusion of Bu_2SnO (entry d) or of either Lewis or protic acids (entry c) served only to reduce the yield of lactam **2.44** from what was obtained without an additive.

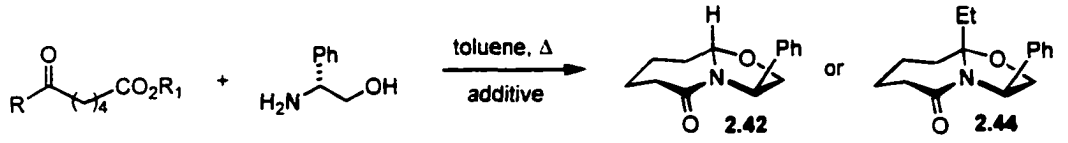


Table 2.7. Additives Surveyed in the Synthesis of Bicyclic Lactams

	R	R_1	Additive*	Outcome
a	H	Me	$CuCl_2$, $PbCl_2$, $NiCl_2$ $MgCl_2$, $FeCl_2$ $AlCl_3$, $SnCl_4$	recovered starting materials
b	H	Me	BF_3•OEt_2, $TiCl_4$	oxazolidine **2.54** (R = H)
c	Et	H	$Cu(OTf)_2$, $ZnCl_2$, $CeCl_3$ TMSOTf, BF_3•OEt_2, $TiCl_4$ TsOH, HCl	yields are lower than without the additive, d.r. remains 2 : 1
d	Et	H	Bu_2SnO	

* Typically used in 10-17 mol %.

The steps involved in the cyclocondensation of a keto acid and amino alcohol to form the bicyclic lactam (a bimolecular step followed by an intramolecular one) are generally considered to be favored by opposite requirements of solvent concentration: relatively concentrated for intermolecular reactions and higher dilution for intramolecular ones. It was therefore decided to try a stepwise approach to the 5,7 lactam, in which each of these processes could be individually optimized. First, the amide bond was formed in 70% yield by reaction of 6-oxooctanoyl chloride with phenylglycinol in CH_2Cl_2 (Figure 2.11). In retrospect, it comes as no surprise that dehydration of **2.60** produced oxazoline **2.61** to the exclusion of lactam **2.24**, since the nucleophilic character of the amide nitrogen in **2.60** is significantly reduced, and reaction through the amide oxygen to form the 5-membered oxazoline is certainly favored kinetically.

Although the strain energy contained in cycloheptane is barely different from that found in cyclopentane (both are ~7 kcal/mol), the rates of cyclization to rings of these sizes are widely different, as the probability that the two reactive termini will become

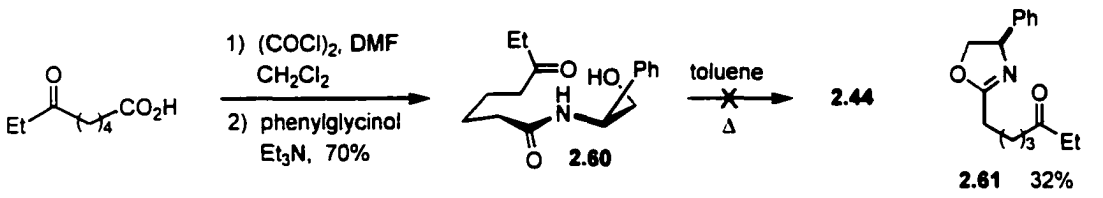
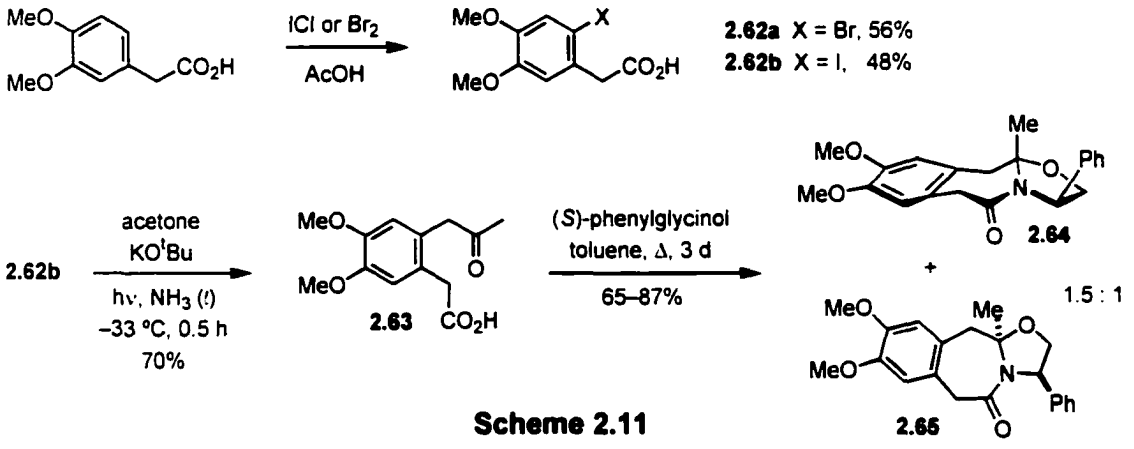


Figure 2.11. Attempted stepwise formation of the bicyclic lactam from keto amide **2.60**

sufficiently proximal is much lower for the 7-membered ring closure.[24] In this regard, it was decided to explore the effect of a conformational restraint, such as a *cisoid* double bond, and its impact in facilitating 7-membered ring closure. Benzo-fused keto acid **2.63** was known in the literature,[26] and its synthesis was performed as outlined in Scheme 2.11.

Halogenation of homoveratric acid proceeded in the 5-position to provide bromide **2.62a**[27a] after a reaction time of 24 hours, or iodide **2.62b**[27b] after 1 week, in moderate yields (Scheme 2.11). Bromide **2.62a** reacted with acetone in an $S_{RN}1$ reaction manifold to produce keto acid **2.63** in trace amounts. It is known that iodide is a better leaving group than bromide for the $S_{RN}1$ reaction,[26] and, in the event, keto acid **2.63** was obtained from **2.62b** in 70% yield. As predicted, phenylglycinol derived benzo-fused lactams **2.64** and **2.65** were obtained in good chemical yield (65–87%), however, the ratio of **2.64**:**2.65** was slightly worse at 1.5 to 1.



Scheme 2.11

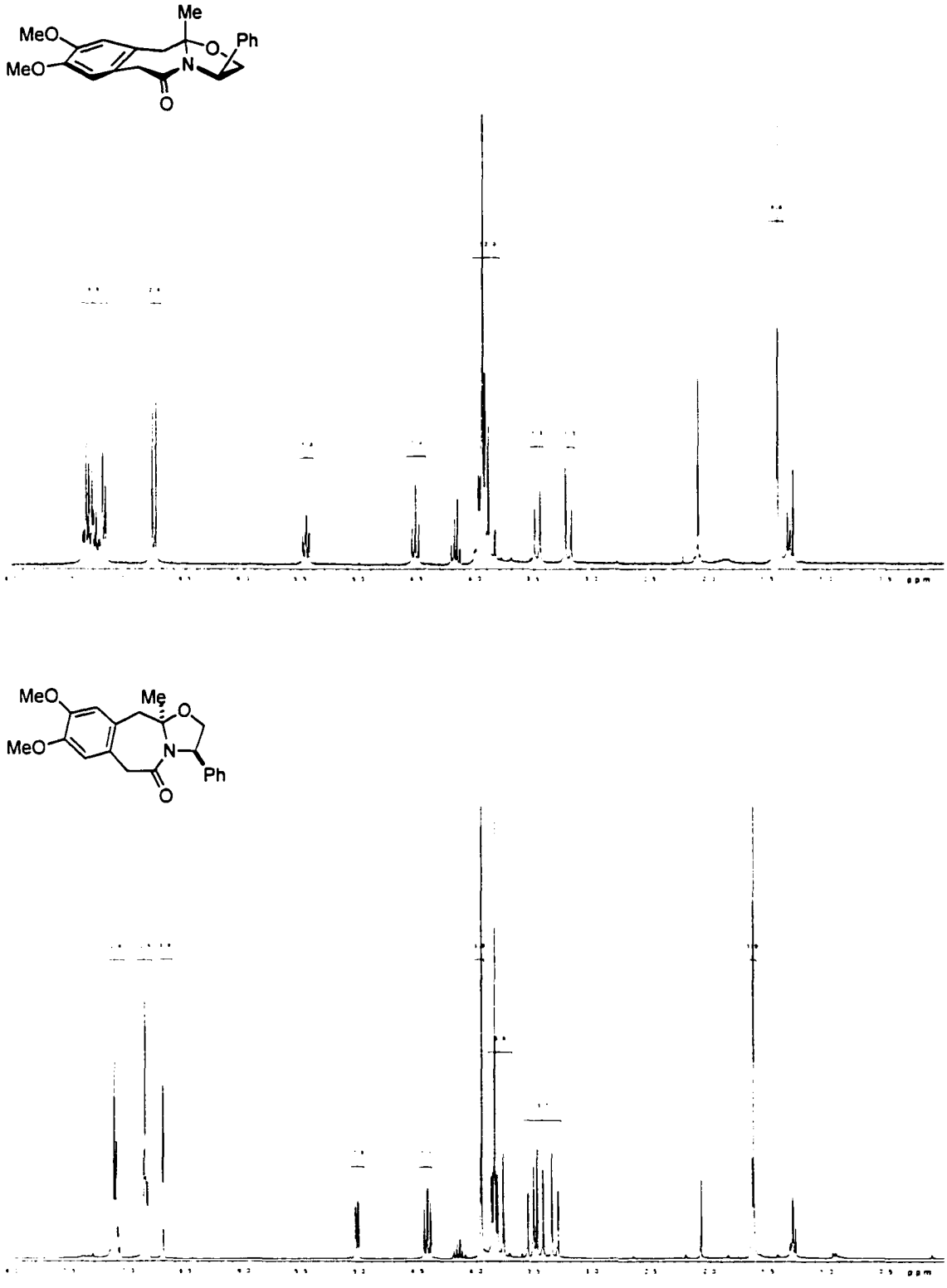


Figure 2.12. 300 MHz ^{1}H NMR spectra of **2.64** (top) and **2.65** (bottom)

For lactams **2.64** and **2.65**, the NMR resonance for the benzylic proton of the chiral auxiliary was again down field (5.42 ppm) in the major diastereomer compared to that for the minor diastereomer (4.99 ppm), but other spectral features of this compound left little room for comparison to lactams **2.48** and **2.20** (Figure 2.12). Specifically, there are fewer protons on the benzo-fused 7-membered ring and the unsaturation serves to change their chemical shift, significantly altering how they appear compared to the other 5,7-lactams. Therefore, the absolute stereochemistry of the major compound **2.64** was assigned from a crystal structure.[17] Although the angular center of lactam **2.64** does have the *exo* disposed methyl group (C-13 in Figure 2.13), the solid state structure is somewhat different from that of lactam **2.48**. Namely, the benzo-fused lactam **2.64** resides in a boat conformation, with the fused aromatic ring folded up, toward the angular methyl group.

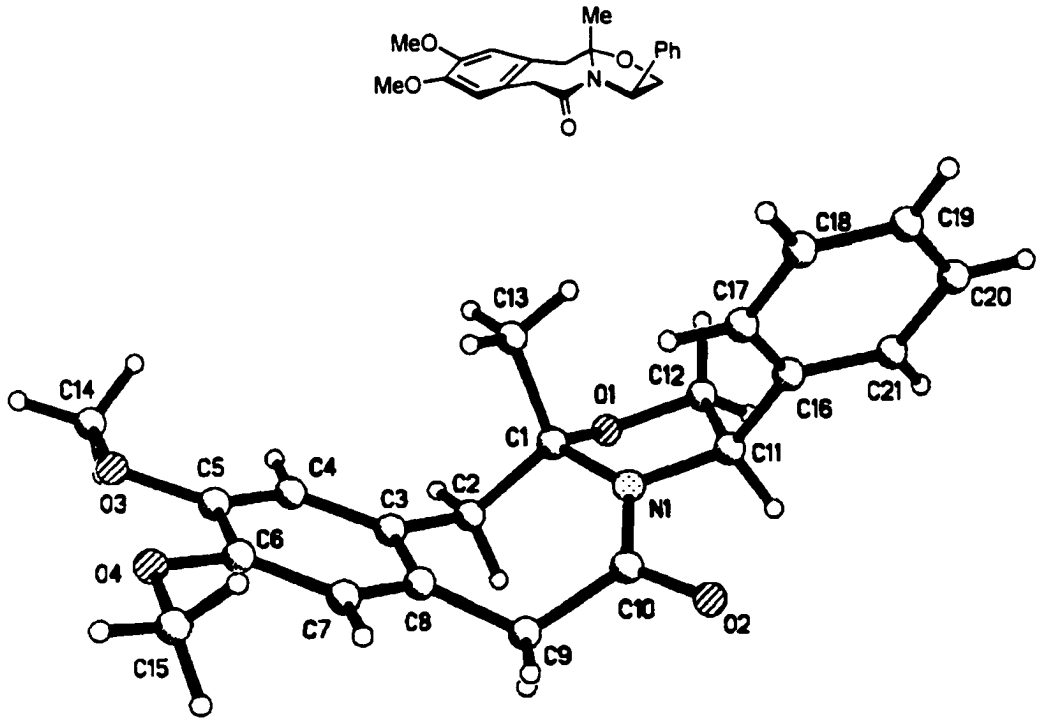


Figure 2.13. Single crystal X-ray structure for compound **2.64**.[17] A disordered solvent molecule (Et_2O) has been removed for clarity.

An alternative route to the 5,7-system was envisaged to take advantage of the high yields and good to excellent diastereoselectivity found in the 5,5- and 5,6-bicyclic lactam syntheses. The two carbon ring expansion of a 5,5-lactam is outlined in Figure 2.14 (EWG = electron withdrawing group). Lithium halogen exchange of a disubstituted lactam such as **2.67** would provide the primary anion, which upon addition into the lactam carbonyl,[28] would produce the strained 5,5,4-tricyclic species **2.68**. Deprotonation of the tertiary alcohol would hopefully be followed by regeneration of the lactam carbonyl and concomitant cleavage of the carbon–carbon bond.[29] The electron withdrawing group in **2.69** would serve to stabilize the rearranged anion until it is quenched. This strategy has been employed in the cleavage of a symmetrical bicyclo[4.2.0]octane ring system to generate the cyclic 8-membered ketone that has been expanded by two carbons.[30] For the system in question, it was unclear what effect the presence of the heteroatoms, the strain of the bicyclic system, or the *endo*- versus *exo* -approach of the anion to the carbonyl would have in these experiments.

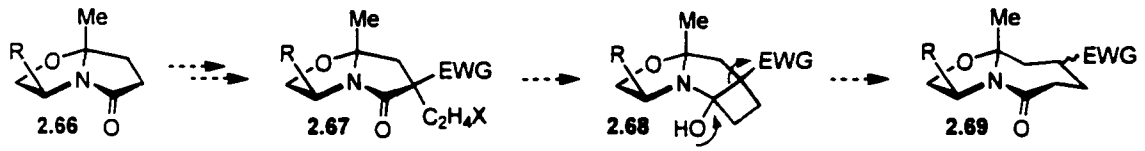
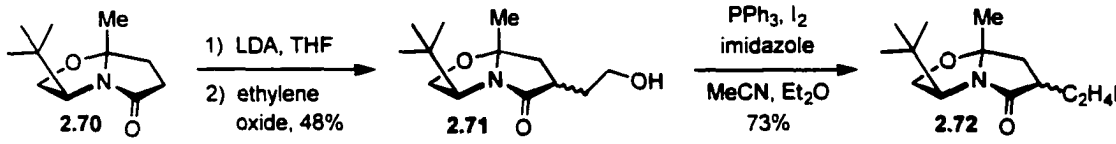


Figure 2.14. Suggested two carbon expansion of the 5,5-bicyclic lactam system

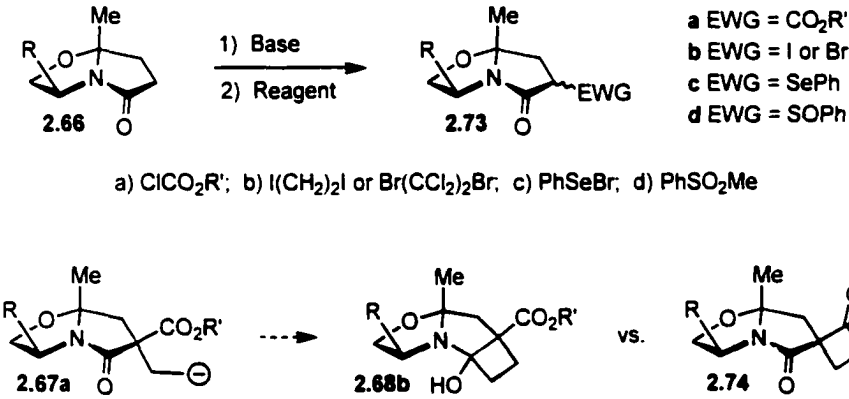
Early studies focused on incorporation of the C_2H_4X moiety into the 5,5-bicyclic lactam, **2.70**. Alkylation of the lactam with 1,2-dibromoethane or (2-bromoethoxy)-*tert*-butyldimethylsilane failed to provide the desired product, and the starting lactam was recovered in low yield (not shown). It was suspected that the former reagent could alternatively serve as a source of electrophilic bromine (expelling ethylene gas and bromide anion), so it was therefore decided to use a two step procedure to effect the desired transformation. The successful synthesis of iodoethyl lactam **2.72** proceeded



Scheme 2.12

as shown in Scheme 2.12. The lithium enolate of lactam **2.70**[1a] was first alkylated with ethylene oxide to afford hydroxyethyl lactam **2.71** in 48% yield.[31] Subsequent reaction with triphenylphosphine, iodine, and imidazole provided iodide **2.72** in 73% yield.[32]

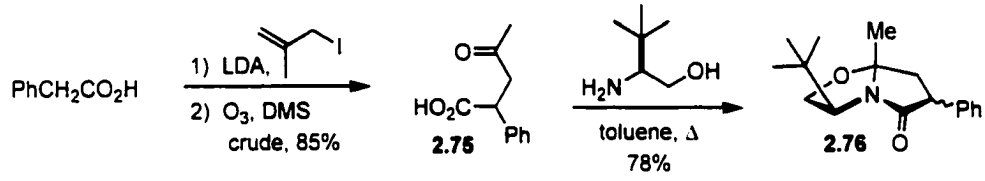
Relatively few electron withdrawing groups have commonly been installed into the α-position of bicyclic lactams. For example, addition of the following electrophiles are known: chloroformates, 1,2-dihaloethanes, selenyl halides, and methyl phenylsulfinate (*vida supra*). These provide **2.73a–d** (α-esters, halides, selenides, or sulfone, respectively, Scheme 2.13). These groups, however, would be unsuitable for the planned expansion of lactam **2.68** via **2.67a**. Intramolecular anion addition into the ester carbonyl in **2.67a**, to produce the spirocyclic ketone **2.74** rather than the desired tricyclic system **2.68b**, seems a likely problem, and the α-phenyl sulfone could suffer the same fate. Similarly, the α-halide would be unsuitable, as a halogen-metal exchange would simply result in reduction of this functionality.



Scheme 2.13

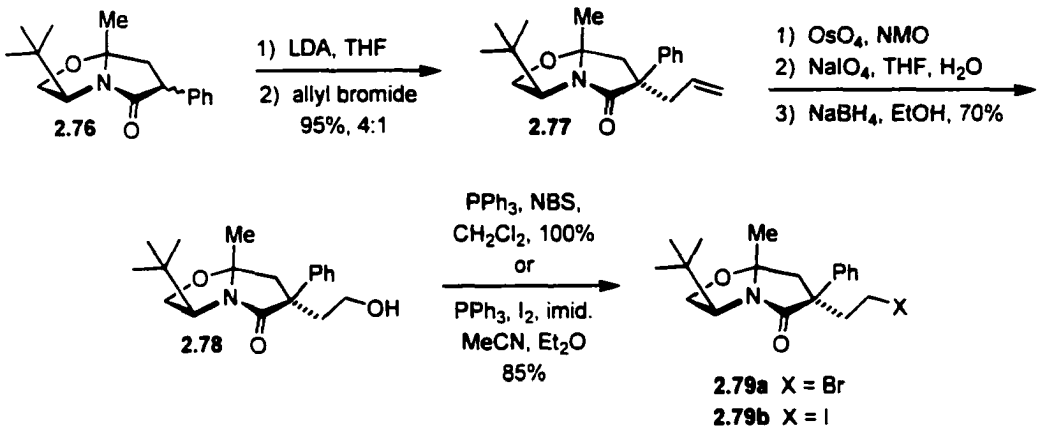
What is required, then, is an α-electron withdrawing group that is expected to be inert to these unwanted side reactions. Two such functionalities are phenyl and cyano, though there are few methods for directly installing these in an "alkylation" step.[33,34] For instance, direct cyanation of the enolate anion of phenylglycinol-derived lactam **2.66** (Scheme 2.13, R=Ph)[3a] with tosyl cyanide[34] failed to produce α-cyano lactam **2.73** (EWG=CN).

Thus, it was decided to synthesize the bicyclic lactam from a keto acid that already had the electron withdrawing group in place (Scheme 2.14). For this purpose, the dianion of phenylacetic acid was first *C*-alkylated with 3-iodo-2-methylpropene, and then the double bond was ozonolyzed to provide the requisite keto acid **2.75** in 85% yield.[35] Lactam **2.76** was obtained in 78% yield after heating **2.75** with *tert*-leucinol in toluene.



Scheme 2.14

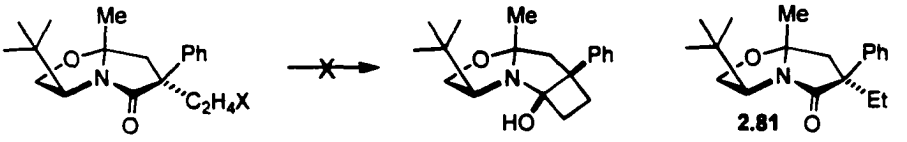
Because the alkylation of lactam **2.70** with ethylene oxide was low yielding, it was decided to use the multistep procedure outlined in Scheme 2.15 to install the hydroxyethyl moiety. Treatment of epimeric lactam **2.76** with LDA generated the planar enolate anion which was alkylated with allyl bromide to produce lactam **2.77**, as a 4 to 1 mixture of epimers, in 95% yield. Generally, strong shielding by an *exo*-α-aryl group causes a significant (0.4 ppm) upfield shift of the resonance for the angular methyl group protons that serves as a diagnostic tool for epimer identification.[1a,35] However, the allyl group also produces this effect, and so renders the ^{1}H NMR data



Scheme 2.15

inconclusive.[36a] Therefore, the major epimer was tentatively assigned structure **2.77** based upon the known tendency for the alkylation of these systems to occur predominantly on the *endo* face.[1a] Lactam **2.77** was next subjected to the following reaction manifold to produce lactam **2.78** in 70% overall yield: dihydroxylation of the double bond with OsO_4 and 4-methylmorpholine *N*-oxide, cleavage of the diol with $NaIO_4$, and reduction of the resultant aldehyde with $NaBH_4$. Hydroxyethyl lactam **2.78** was converted to bromide **2.79a** in quantitative yield by treatment with PPh_3 and *N*-bromosuccinimide,[28] or to iodide **2.79b** in 85% yield by treatment with PPh_3, iodine, and imidazole. Now that the allyl group is gone, the upfield resonance for the angular methyl group protons of compounds **2.78**, **2.79a**, and **2.79b** serve to verify that the stereochemistry of these compounds is correct as shown.[36b]

The results of several experiments attempting the construction of tricyclic expansion precursor **2.80** from lactams **2.79a** and **2.79b** are described in Table 2.8. The lithium bromide exchange of lactam **2.79a** with *t*-butyl lithium was performed in THF and provided, after quench, 23% of reduced lactam **2.81** and 71% of α-monosubstituted lactam **2.76** (entry a). In this case, elimination of ethylene gas with simultaneous formation of the delocalized lactam anion serve to make dealkylation an energetically



2.79a X = Br
2.79b X = I

2.80

Table 2.8. Attempted Construction of the Tricyclic Expansion Precursor

	Halide	Reagent	Conditions		**2.81**	Other
a	**2.79a**	*t*-BuLi	THF	–78 °C, 1 h	23% +	**2.76** (71%) 1 diastereomer
b	**2.79a**	*t*-BuLi	Trapp	–100 °C, 4 h; then –80 °C, 4 h	23%	
c	**2.79b**	SmI_2 + HMPA	THF	–78 to 0 °C, 0.5 h; then rt, 1.5 h	27% +	**2.79b** (48%)
d	**2.79b**	SmI_2 + HMPA	THF	–78 °C to rt, 12 h; then reflux, 20 h	33% +	**2.79b** (17%)
e	**2.79b**	SmI_2 + $Fe(acac)_3$	THF	–78 °C to rt, 28 h		**2.79b** (89%)
f	**2.79a**	*n*-Bu_3SnH + AIBN	PhH	reflux, 3 d	51%	
g	**2.79a**	*n*-Bu_3SnH + AIBN	mesitylene	reflux, 12 h	decomposed	

Trapp solvent = 4:1:1 THF/Et_2O/pentane

favorable process. It was hoped that ethylene expulsion would be slower at a lower temperature relative to the rate of anion addition into the carbonyl, and therefore the reaction was repeated at –100 °C (entry b). However, no reaction occurred at this temperature, and after 4 hours at –80 °C, reduced **2.81** was again isolated.

Acyl displacements of amides and esters with pendant primary radicals have been reported to afford 4-, 5-, and 6-membered cyclic ketones.[37] It was anticipated that, in the present system, the strained carbon–carbon bond would serve as a better leaving group than the oxazolidine ring[28] (which would thereby produce a cyclobutanone). Therefore, several experiments were explored using radical chemistry for the construction of **2.80**. The low temperature reduction of iodide **2.79b** with SmI_2 and hexamethylphosphoramide[37] was followed by stirring at room temperature (Table 2.8,

entries c,d). After 1.5 hours, 27% of reduced lactam **2.81** and 48% of starting iodide **2.79b** were obtained (entry c). Believing that addition into the acyl group stood a better chance of success at an elevated temperature, this last reaction was repeated with heating at 65 °C (entry d). After stirring 20 hours at reflux, however, the result was not substantially different from that obtained in entry c. The use of iron (III) acetylacetonate[37] as the additive returned only unreacted starting material after 28 hours at room temperature (entry e). To increase the temperature further, the reduction of bromide **2.79a** was carried out with tri-*n*-butyltin hydride in benzene at reflux. After 3 days, reduced lactam **2.81** was produced in 51% yield (entry f).[38a] It was thought that *n*-Bu_3SnH may be further reducing the primary radical before it had a chance to react with the lactam carbonyl, however, the slow addition of *n*-Bu_3SnH and AIBN over 3 hours did not improve matters (entry g).[38b]

Through these experiments, it remains unclear whether the difficulty in formation of **2.80** resides in steric congestion for the approach to the *endo*-face of the lactam carbonyl, an unfavorable electronic situation surrounding addition into the carbonyl, or whether it is simply a matter of the low rate reported for 4-*exo*-trig ring closure.[39] In these 5.5-bicyclic systems, the nitrogen atom is frequently found to be highly pyramidalized,[40] and the carbonyl thus maintains significant ketonic character. In fact, the IR frequency for the carbonyl of lactam **2.78** was 1704 cm^{-1}, and it seems, therefore, that the carbonyl group should be sufficiently electron-deficient so as to undergo nucleophilic addition. Often, the disubstituted bicyclic lactams with reversed α-carbon substitution can be obtained by changing the order of addition of the electrophiles to the lactam anion.[1a] Given the special synthesis required for the keto acid used in these experiments, the C-1 epimer of lactam **2.78** is inaccessible and it remains difficult to

assess whether approach of the pendant anion or radical to the *exo*-face of the carbonyl would be more favorable.

The one-carbon ring expansion of the 5,6-bicyclic lactam was investigated more briefly. The simplest of these experiments examined the reaction of (trimethylsilyl)-diazomethane with lactam **2.46** (Figure 2.15); but, only recovered starting material was obtained. Given the known difficulty in addition of alkyllithium and magnesium reagents to the carbonyl of 5,6-bicyclic lactams such as **2.46**,[1a] this experiment was repeated with the (*S*,*S*)-Parke–Davis derived lactam **2.82**,[41] which is known to undergo such additions. Unfortunately, the outcome remained the same.

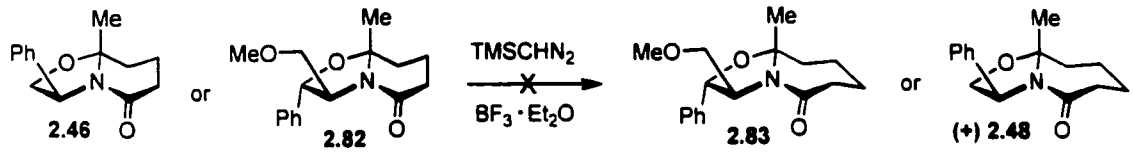
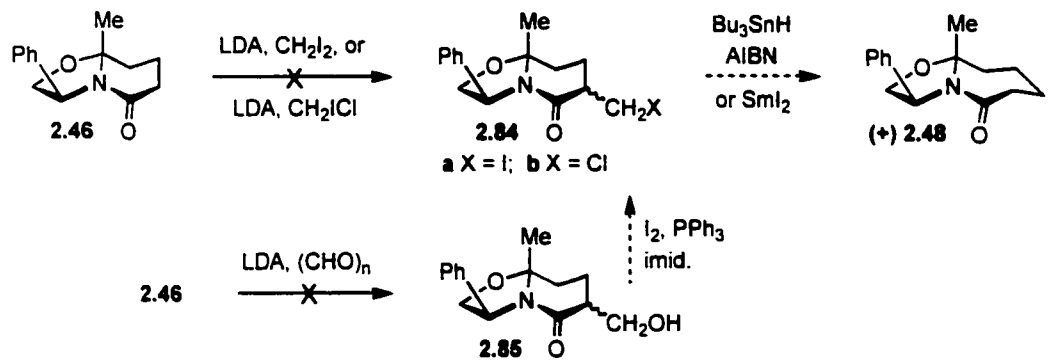


Figure 2.15. Attempted one step expansion using (trimethylsilyl)diazomethane

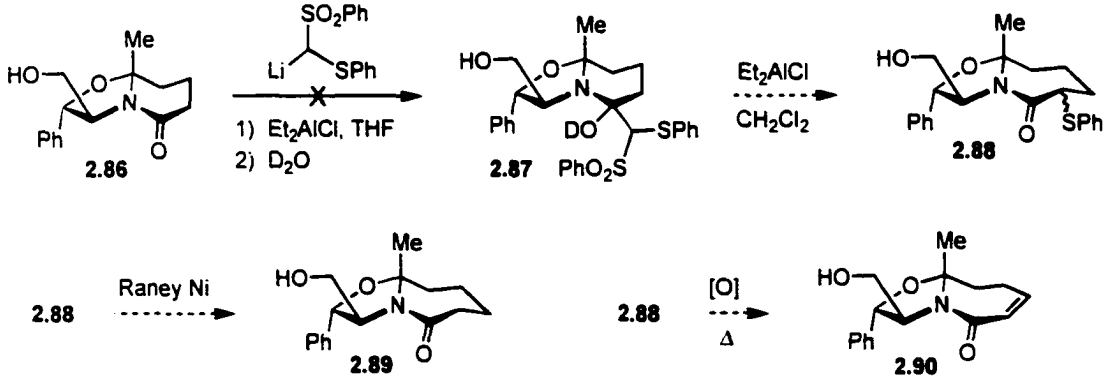
It was believed that 3-*exo*-trig addition into the 5,6-lactam carbonyl would be more facile than 4-*exo*-trig cyclization into the 5,5-lactam carbonyl.[39] Unfortunately, the pivotal α-halomethyl 5,6-lactam **2.84** could not be obtained directly from lactam **2.46** via alkylation with either diidomethane[38c] or chloroiodomethane (Scheme 2.16). Although it seems it should be a simple matter to obtain iodolactam **2.84a** from hydroxymethyl



Scheme 2.16

lactam **2.85**, the single experiment attempting alkylation of lactam **2.46** with paraformaldehyde failed to produce hydroxylactam **2.85**. The complex mixture obtained from this reaction, though not analyzed, was suspected to include a mixture of exocyclic and endocyclic alkene isomers from subsequent elimination of water from the desired product.

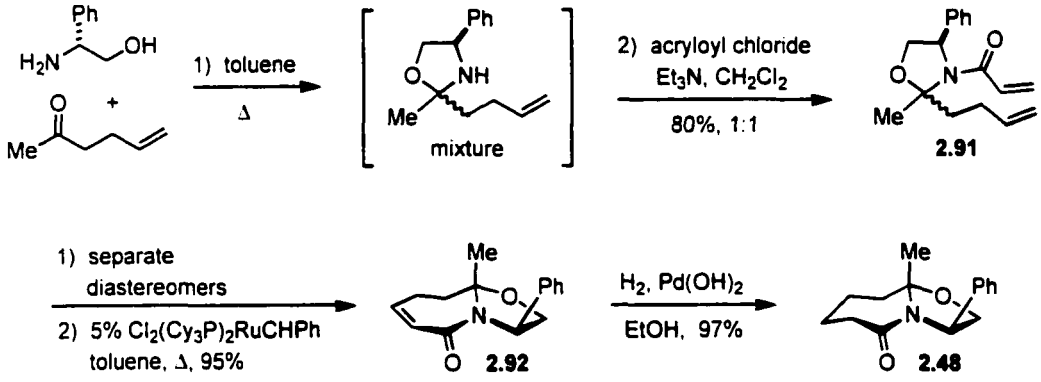
The final set of experiments in this series sought to synthesize the versatile α-thiophenyl 5,7-lactam **2.88** from Parke–Davis lactam **2.86** in two steps (Scheme 2.17). Lactam **2.88** could then be treated with Raney nickel to remove the sulfur moiety and thus reveal lactam **2.89**, or it could be oxidized to produce, after sulfoxide elimination, α,β-unsaturated 5,7-lactam **2.90**. The lithio thiophenyl-phenylsulfinate anion has been shown to add into ketone carbonyls in the presence of the Lewis acid, diethylaluminum chloride, and upon changing the solvent to dichloromethane, these species undergo Lewis-acid-promoted rearrangement to give α-thiophenyl carbonyl systems homologated by one carbon.[42a] When lactam **2.86**[1a] was used as the substrate, lithio phenylthio-phenylsulfinate[42b] proved insufficiently nucleophilic or too sterically demanding to add into the lactam carbonyl, and also insufficiently basic to deprotonate the lactam alpha to the carbonyl. The lack of deuterium incorporation in lactam **2.86**



Scheme 2.17

was noted upon quench with D_2O. From this reaction, lactam **2.86** was recovered in 71% yield and 77% of $PhSCHDSO_2Ph$ was obtained.

Finally, a successful alternative route to 5,7-lactam **2.48** was found (Scheme 2.18).[43] Phenylglycinol and 5-hexen-2-one were heated in toluene with azeotropic removal of water to form the transiently stable oxazolidine ring, which was then treated directly with acryloyl chloride and triethylamine to form *N*-acyl oxazolidine **2.91** in 80% yield. After chromatographic separation of the 1 to 1 diastereomeric mixture, ring closing metathesis with $Cl_2(Cy_3P)_2RuCHPh$ catalyst produced α,β-unsaturated 5,7-bicyclic lactam **2.92** in 95% yield.[44] Lactam **2.48** was obtained in 97% yield after hydrogenation of the double bond over $Pd(OH)_2$.[3acd] While this method does provide an easily scaleable synthesis of lactam **2.48** from readily available precursors, it provides, as predicted, no basis for discrimination among the diastereomers formed in the first step, and the final product is therefore realized in just 37% yield from (*R*)-phenylglycinol.



Scheme 2.18

C. Stereoselective Reductions to 2-Alkyl-Perhydroazepines

With multiple 5,7-bicyclic lactams in hand, the next point of focus was to determine if they would indeed serve as precursors to chiral perhydroazepines. A variety of hydride reducing agents were surveyed in the reduction of angular methyl

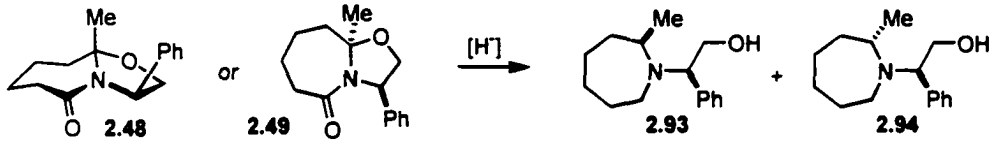


Table 2.9. Hydride Reductions of Angular Methyl Lactams

	Lactam	Hydride Source	Conditions	Yield	**2.93** : **2.94** ^{1}H NMR[3]	HPLC[4]
a	**2.48**	$LiAlH_4$	-78° C → rt, 18.5 h; Δ, 2 h	50%[1]	7 : 1	94.3 : 5.7
b	**2.48**	$LiAlH_4$	Δ, 20 h	88%[2]	10 : 1	
c	**2.48**	AlH_3	-78 °C, 45 min; rt, 15 min	80%	18 : 1	95.7 : 4.3
d	**2.48**	AlH_3	-100 °C → rt, 12 h	90%[2]	6 : 1	
e	**2.48**	*i*-Bu_2AlH	-78 °C → rt, 5 h	93%[2]	1 : 1	
f	**2.48**	Red-Al[5]	0 °C → rt, 7 h	Decomp.		
g	**2.48**	BH_3	Δ, 12 h	89%[2]	3 : 1	
h	**2.48**	9-BBN[6]	rt → Δ, 19 h	Decomp.		
i	**2.48**	L-Selectride[7]	Δ, 2 d	No Rxn		
j	**2.49**	$LiAlH_4$	Δ, 12 h	70%[2]	2 : 1	
k	**2.49**	AlH_3	-78 °C, 45 min; rt, 15 min	51%	1 : 1	
l	**2.49**	*i*-Bu_2AlH	-78 °C → rt, 12 h	95%	1 : 14	4.5 : 95.5

1 Partial reduction product obtained (14%). 2 Yields are crude. 3 From integration of ^{1}H NMR signals (methyl doublets) at 1.17 and 0.97 ppm, respectively; values are approximate due to signal obscuring impurity in samples. 4 From HPLC (Regis (*R,R*) Whelk-02 Pirkle Covalent chiral column) of derivative **2.97d**; values are ±0.5. 5 Red-Al = $Na(MeOC_2H_4O)_2AlH_2$. 6 9-BBN = 9-borabicyclo[3.3.1]nonane. 7 L-Selectride = Li(*sec*-Bu)$_3$BH.

lactam **2.48**, and these are described in Table 2.9. The first reagent studied was alane (entry c), which provided the amino alcohols **2.93** and **2.94**, in good yield (80%), in what appeared by ^{1}H NMR spectroscopy, an approximately 6 to 1 diastereomeric mixture. The major epimer was temporarily assigned structure **2.93** under the assumption that reduction proceeded with retention of the relative stereochemistry, as observed earlier for the 5,5- and 5,6-systems.[3acd] Compounds **2.93/2.94** streaked badly during flash column chromatography; they began to elute in rather non-polar solvent mixtures (hexanes/EtOAc 6:1), and the polarity had to be increased considerably (EtOAc, 100%) in order to remove the remainder of the compound from the silica gel. Additionally, the diastereomers were not separable from each other under these elution conditions, so

the final product was always contaminated with some of the minor reduction product and some other unanalyzed impurity(ies). This reaction was repeated, starting at a lower temperature (entry d), though this did not improve the selectivity. The selectivity was completely eroded by using the bulkier reagent, diisobutylaluminum hydride (entry e), and with Red-Al, the starting material was converted into unrecognizable products (entry f). The use of borane in THF at reflux provided a 3 to 1 mixture of the amino alcohols **2.93/2.94** (entry g). Reduction with 9-BBN was slow at room temperature (entry h), but after heating the mixture, the starting material was converted into unrecognizable products. No reaction occurred at all after prolonged heating of **2.48** with L-Selectride (entry I). Surprisingly, the reduction with lithium aluminum hydride seemed to be about as selective as that with alane (entry a). Eventually, it was found that if the chromatography began with hexanes/EtOAc 10:1, and then changed to EtOAc, most of a higher R_f impurity could be removed, which helped to clarify the ^{1}H NMR spectra to some extent. When the experiment (entry c) was repeated, it was found that the selectivity of the alane reduction was actually far superior (~18:1) than originally believed, though accurate determination awaited further chemical manipulation (*vide infra*).

Use of the improved reduction conditions for lactam **2.48** failed to produce appreciable selectivity in the reduction of the minor lactam diastereomer **2.49** (Table 2.9, entries j,k), however, in a serendipitous discovery, DIBAL reduction of **2.49** was quite selective, furnishing amino alcohol **2.94** preferentially (entry l).

In the purification of piperidine amino alcohols **2.5** (Scheme 2.3, p 64, n=2) it was necessary to convert the product mixture to the acetyl esters in order to separate the minor diastereomer by chromatography.[3d] However, for the azepine acetyl derivative **2.95a**, separation of the minor reduction product could not be achieved using

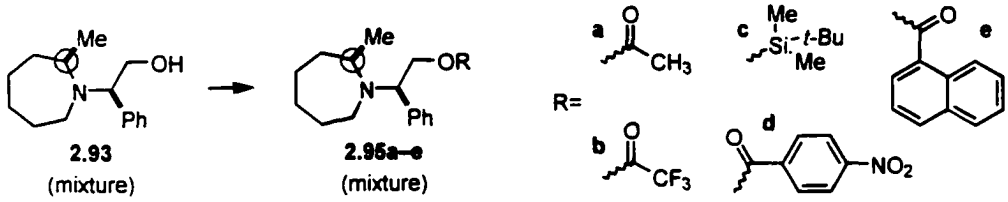


Figure 2.16. Amino alcohol derivatives were inseparable via flash or HPLC chromatography

flash chromatography. Other derivatives experienced the same problem (Figure 2.16). These compounds were quite non-polar and eluted with 100% hexanes, without separation, from the normal phase HPLC column as well.

It was, therefore, decided to cleave the benzyl moiety (H_2, $Pd(OH)_2$, EtOH) and explore the separation of racemic derivatives **(±)-2.97a–d** on chiral HPLC columns (Figure 2.17). The brosyl, tosyl, and 2,4,6-trichloro derivatives **(±)-2.97abc** had the same polarity problem as the derivatives above, eluting from the column (Chiracel OB, OJ, OD) in non-polar solvent mixtures (0-0.1% isopropanol in hexanes), without clear separation. Finally, the enantiomers of the p-bromobenzoyl derivative **(±)-2.97d** were separated (Whelk-02 Pirkle Covalent), and it was then possible to assign accurate product ratios in the reduction of bicyclic lactams **2.48** and **2.49** (Table 2.9). Thus, it was found that reduction of **2.48** with alane was slightly more selective (95.7:4.3) than was reduction with $LiAlH_4$ (94.3:5.7). Additionally, the absolute stereochemistry at *C*-2

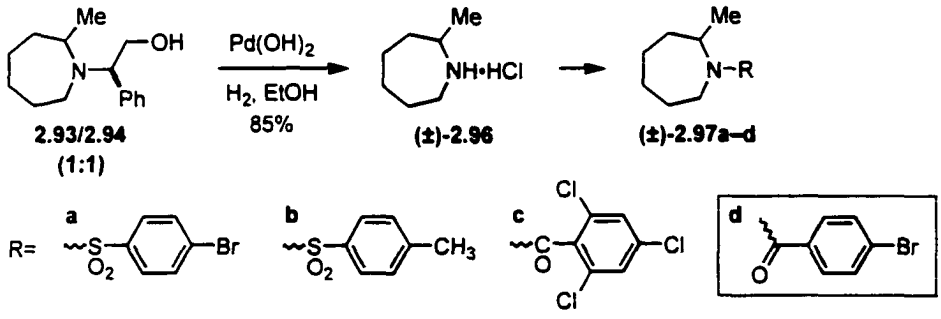


Figure 2.17. Enantiomeric mixture **(±)-2.97d** was separated by chiral HPLC

of the amino alcohol **2.93** obtained in these reductions was discovered to be *R* from the crystal structure of the hydrochloride salt **(–)-2.96**.[45]

Table 2.10 describes the stereoselective hydride reductions of the angular ethyl bicyclic lactams **2.44** and **2.45**. The reaction of $LiAlH_4$ with **2.44** proceeded in good yield and, by ^1H NMR spectroscopy, the reaction was obviously selective (entry a). Even approximate quantification of the product ratio was not feasible, however, because all potentially diagnostic signals were at least partially overlapping. Therefore, a mixture of amino alcohols **2.98** and **2.99** (approx. 1:1) was subjected to hydrogenolytic cleavage of the benzylic group, using the same conditions as before (Figure 2.18), and then transformed into the p-bromobenzoyl derivative **2.101/2a** with hopes of obtaining the reduction ratio from chiral HPLC chromatography. The enantiomers could not be separated, however, using the conditions found for **(±)-2.97d**. Thus, it was decided to synthesize the ureas **2.101/2b** (from (*S*)-α-methylbenzyl isocyanate, 50% over 2 steps) from which the reduction selectivity in reaction a was determined (Chiracel OD column) to be 88.6:11.4.

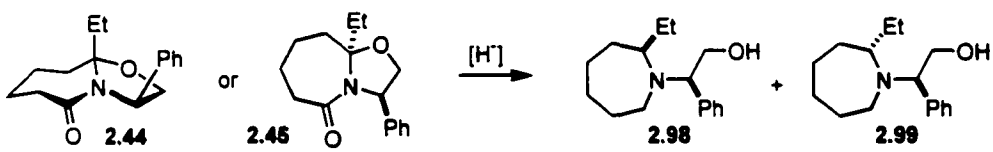


Table 2.10. Hydride Reductions of Angular Ethyl Lactams

	Lactam	Hydride Source	Conditions	Yield	**2.98** : **2.99**[2]
a	**2.44**	$LiAlH_4$	-78° C → rt, 20 h; Δ, 8 h	83%	88.6 : 11.4
b	**2.44**	AlH_3	-78° C → -20° C, 17 h; rt, 22.5 h; Δ, 15 min	51%[1]	92.0 : 8.0
c	**2.45**	*i*-Bu_2AlH	-78 °C → rt, 19 h	61%	3.2 : 96.8

1 Reaction did not go to completion; partial reduction product obtained. 2 From appearance of partially coalesced ^1H NMR signals (methyl triplets) at 0.89 and 0.82 ppm, each reduction gave mostly one product. Therefore, ratios are from HPLC (Chiracel OD column) of urea derivative **2.101b/2.102b**; values are ±0.5.

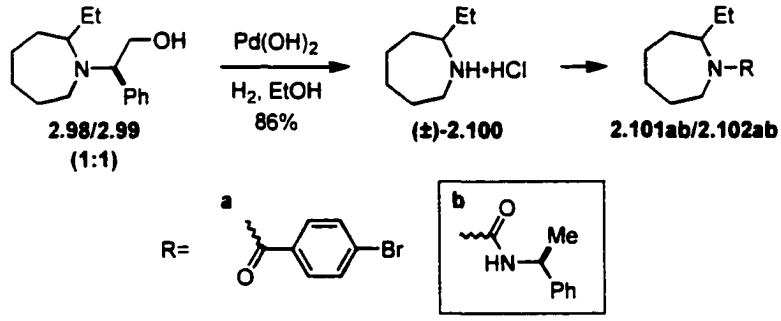


Figure 2.18. Diastereomeric mixture **2.101b/2.102b** was separated by chiral HPLC

Reduction of **2.44** with alane was slightly more selective (92.0:8.0) than with $LiAlH_4$, but the reaction had not gone to completion after 2 days (Table 2.10, entry b). Reduction of *endo* lactam **2.45** with DIBAL provided a 3.2:96.8 mixture of amino alcohols **2.98/2.99** in moderate yield (entry c).

The stereochemistry obtained in the reduction of *exo*-ethyl lactam **2.44** was shown to be the same as that for reduction of the angular methyl bicyclic lactam **2.48** by comparison of the circular dichroism spectra of amino alcohols **2.93** and **2.98** (Figure 2.19). Because these compounds have two chiral centers, it was not at first known with certainty that this method would be suitable for discerning diastereomers. As shown in the figure, **2.93** and **2.98** show very similar Cotton effects, however, amino alcohol **2.99**, of opposite configuration at *C*-1, does indeed have an appreciably different appearance. This data serves as a strong indication of this method for epimer comparison.

The $LiAlH_4$ reduction of *exo*-benzo-fused lactam **2.64** followed the trend of selective reduction, providing a 95:5 mixture of epimeric amino alcohols **2.103** and **2.104**, but in moderate and variable yields (Table 2.11, entry a). This time, the product ratio was easily discerned by integration of the ^1H NMR signals for the methyl doublets. Unlike for *exo* lactams **2.48** and **2.44**, use of alane in the reduction of **2.64** provided only

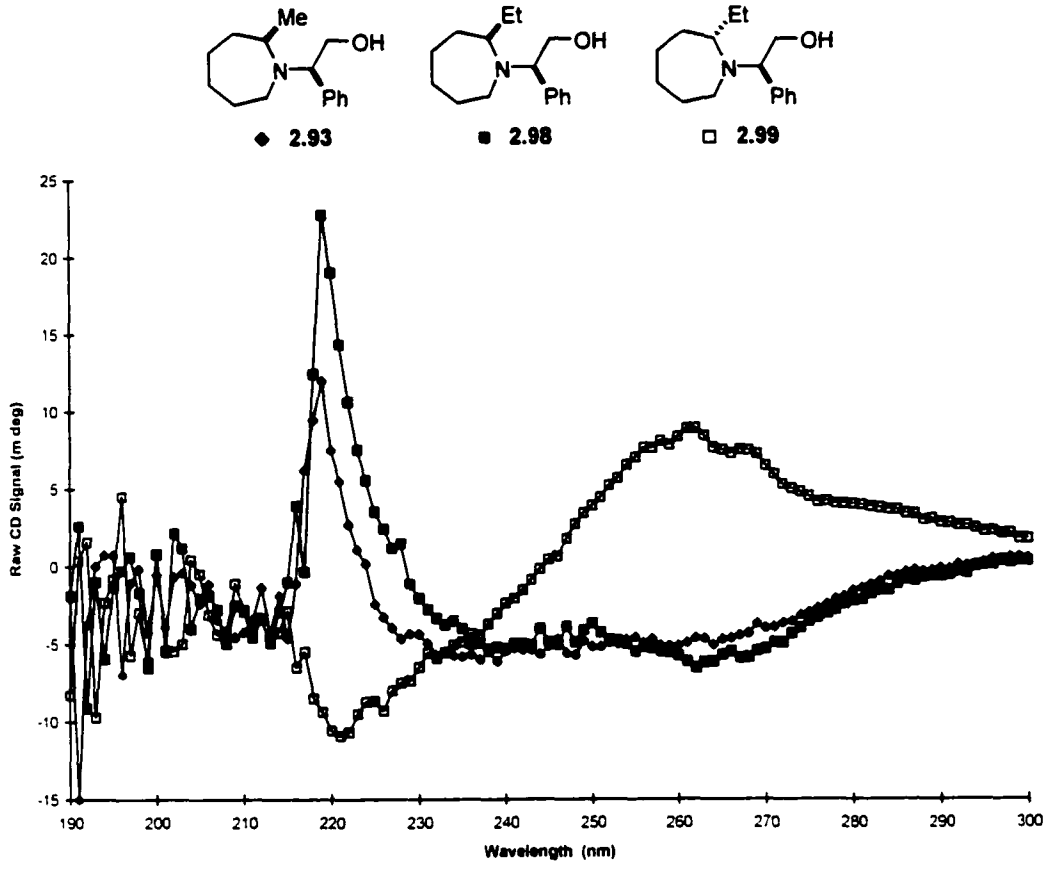


Figure 2.19. Circular dichroism (CD) spectra of amino alcohols **2.93** and **2.98/2.99** in CH_3CN

a trace amount of amino alcohol products, with virtually no selectivity (entry c). The major product identified from this reaction was the benzazepinone alcohol, obtained from reduction of only the angular center of bicyclic lactam **2.64** (20%, not shown). Reductions of the *endo* lactam **2.65** with $LiAlH_4$ and alane were slightly more selective at 1:3 and 1:4, respectively, than those observed for *endo*-methyl lactam **2.49**. However, once again, DIBAL reduction of the *endo* lactam was rather selective, providing amino alcohols **2.103** and **2.104** in a ratio of 3:97, in 53% chemical yield.

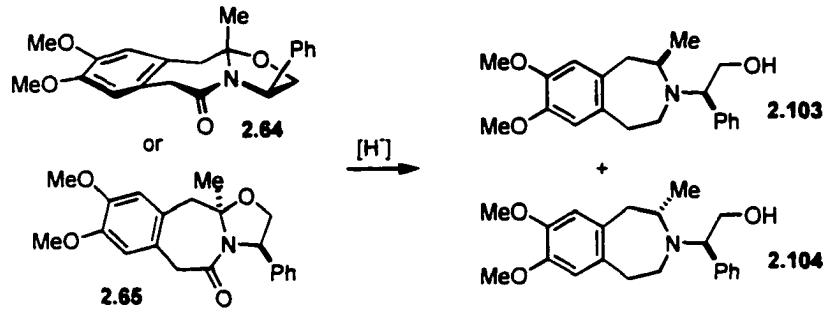


Table 2.11. Hydride Reductions of Benzo-fused Lactams

	Lactam	Hydride Source	Conditions	Yield	**2.103** : **2.104**[1]
a	**2.64**	$LiAlH_4$	rt, 29 h	27–50%	95 : 5
b	**2.64**	AlH_3	-78 °C → rt, 16 h	No Rxn	
c	**2.64**	AlH_3	rt, 37 h	10%	60 : 40
d	**2.65**	$LiAlH_4$	rt, 18 h	43%	25 : 75
e	**2.65**	AlH_3	Δ, 12 h	27%	20 : 80
f	**2.65**	*i*-Bu_2AlH	-78 °C → rt, 27 h	53%	3 : 97

1 From integration of ^1H NMR signals (methyl doublets) at 0.78 and 0.72 ppm, respectively; values are ±2%.

Circular dichroism spectra of amino alcohols **2.103** and **2.104** were taken (Figure 2.20), in order to see if the trace for **2.103** would correlate with that for **2.93**, thus demonstrating that all of the *exo*-5,7-bicyclic lactams were reduced with the same absolute stereochemistry. As is evident from Figure 2.20, no meaningful comment can be made about the stereochemical outcome of the benzo-fused reductions from this data. In the correlation of closely related families of products, it has been reported that comparison must be made between products of the same conformation, since it is not just the configurations of the centers but also the spatial distribution of the atoms which is important.[46] That the CD spectra in the present case look quite different is not surprising given that bicyclic benzo-fused amino alcohols **2.103/2.104** probably do not comprise a homologous conformational series with monocyclic amino alcohols **2.93/2.94/2.98/2.99**.

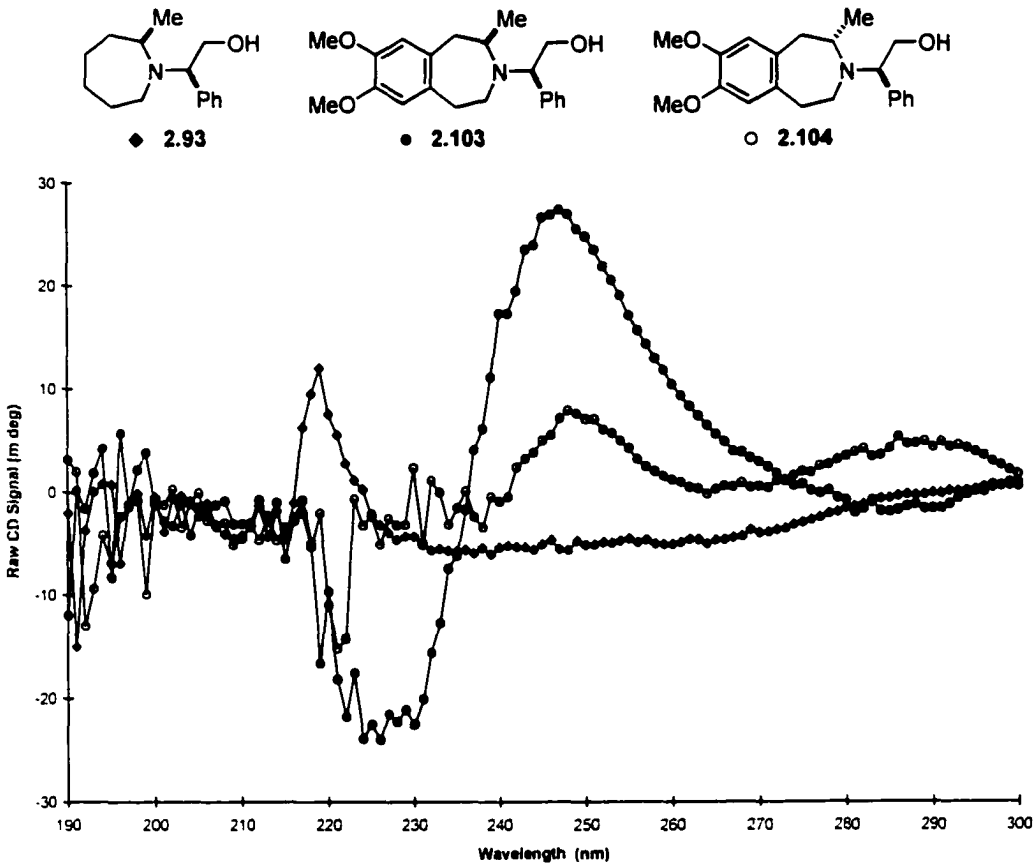
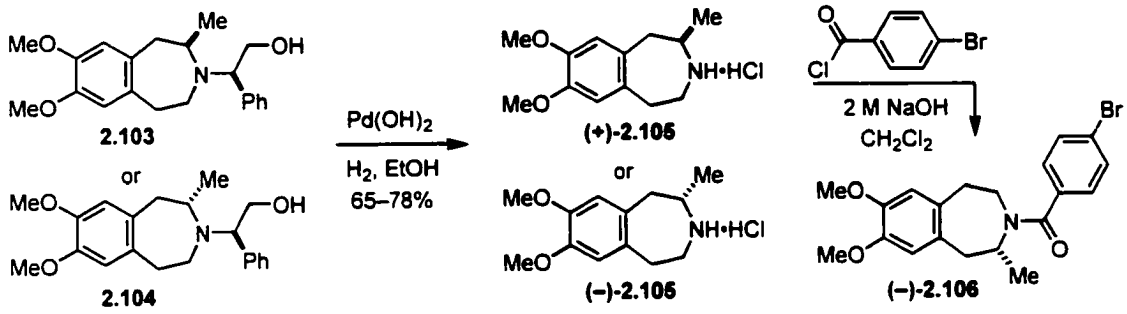


Figure 2.20. CD spectra of amino alcohols **2.93** and **2.103/2.104** in CH_3CN

Hydrogenolysis of either *N*-benzyl compound **2.103** or **2.104** provided access to chiral benzazepine **(+)-** or **(–)-2.105**, respectively, in good yields (Scheme 2.19). At this point, an opportunity presented itself to make a comparison between the p-bromobenzoyl derivative **(–)-2.97d** and the analogous benzazepine derivative **(–)-2.106**, both obtained from reduction of the parent *exo* bicyclic lactams. With only one stereocenter present in these molecules, the presence of either a positive or a negative Cotton effect should be sufficient to establish whether the absolute configurations were the same. Thus, **(+)-2.105** was treated with p-bromobenzoyl chloride under Schotten–Baumen conditions to provide required derivative **(–)-2.106** in an un-optimized 33% yield. As presented in Figure 2.21, the CD spectra of derivatives **(–)-2.97d** and



Scheme 2.19

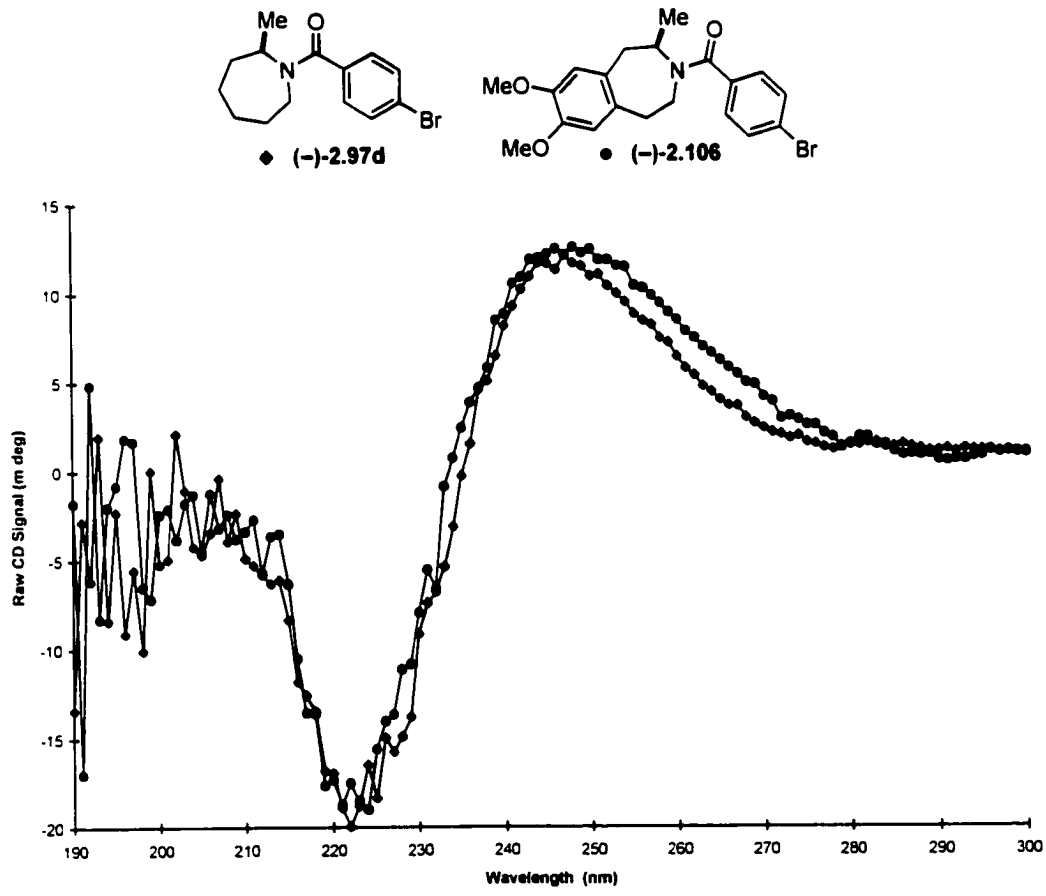


Figure 2.21. CD spectra of p-bromobenzoyl amides **(–)-2.97d** and **(–)-106** in CH_3CN

(–)-2.106 are remarkably similar, and suggest strongly that reduction proceeds in the same stereochemical sense for each of the *exo*-5,7-bicyclic lactams studied.

Rationalization for the stereochemical outcome in hydride reductions of the *exo*-5,7-bicyclic lactams follows directly from that which was reported earlier for the reduction of 5,5- and 5,6-bicyclic lactams with alane.[3acd] The reader is referred to pages 64–65 for that discussion. Prior to this project, however, stereoselective reductions of the minor, *endo*-bicyclic lactam diastereomers had not been reported, and a few comments in regard to this topic are pertinent.

As with the other lactams, following reduction of the amide to the amine, coordination of the aluminum reagent to the remaining oxygen facilitates formation of an iminium-ion intermediate **C** (Figure 2.22), which is trapped in an intramolecular sense by the coordinated aluminum reagent before complete planarity of the angular center, or complete scission of the C–O bond, is realized. The result is "retention" of the relative stereochemistry about the angular carbon center. Should the aromatic ring of the chiral auxiliary reside in a pseudo-equatorial position, it does appear, in molecular models, that the β-face of the bicyclic structure is the more accessible one. When the majority of interactions occur on this face, high selectivity should be observed.

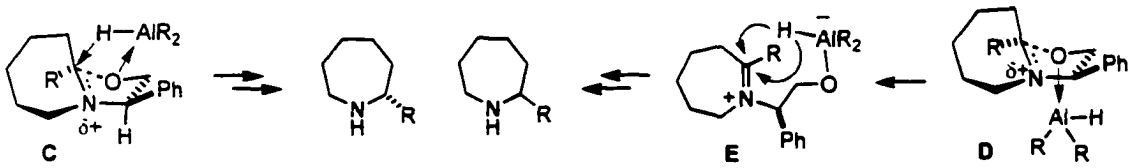


Figure 2.22. Origins of selectivity in DIBAL reductions of *endo*-5,7-bicyclic lactams

Given the proposed intramolecular nature of the reduction, however, it seems that coordination of the aluminum reagent need not occur strictly on one face of the bicyclic structure for "retention" of the stereochemistry to be observed. When

coordination occurs on the α-face, as in **D**, it may be the timing of hydride delivery that is important (Figure 2.22). If intramolecular reduction is slow for some reason, (perhaps because the one hydride equivalent on DIBAL is not sufficiently proximal to the reactive center for reduction to occur promptly), formation of the imine bond may lead to a discreet intermediate **E**, containing a planar center, that is then reduced either by the complexed aluminum reagent in an intramolecular, but not stereoselective, sense, or by a second equivalent of reagent in an intermolecular fashion. Either way, erosion of selectivity would be observed. Given the high selectivity observed in these reactions, and the bulky character of the aluminum reagent employed, it is suggested that the majority of interactions occur from the β-face of the bicyclic system.

E. Summary

The project reported herein describes the synthesis and utility of a novel class of compounds, the 5,7-bicyclic lactams, which possess various biological properties. These structures were produced by the cyclodehydration of (*R*)-phenylglycinol with ω-keto acids to provide the methyl and ethyl compounds as separable diastereomeric mixtures at the angular center (~2:1) in low yields (~40%). Several efforts were made to improve upon both the yield, and the diastereoselection of bicyclic lactam formation, including the attempted synthesis of the adipimide **2.52**, the use of Lewis-acid additives, and the proposed expansion of 5,5- and 5,6-bicyclic lactams. Though these experiments failed, it was found that use of the conformational constraint provided by a *cis*-alkene in the keto acid backbone served to improve the chemical yield (to 65–87%) obtained from the cyclodehydration method. In the one case examined, the diastereoselection was found to be slightly reduced. Additionally, it was found that the angular methyl bicyclic lactam could be synthesized in high chemical yield using ring

closing metathesis. However, since the precursor *N*-acyl oxazolidine **2.91** was formed with poor selectivity, the usefulness of this route is diminished.

Stereoselective reductions of the 5,7-bicyclic lactams proceeded smoothly with the use of alane or lithiumaluminum hydride, affording amino alcohols of the *R* configuration at the 2-position, in good to moderate yields (50–88%) from the *exo* epimers. Selectivity was also found in the diisobutylaluminum hydride reduction of the *endo* lactam epimers, affording amino alcohols of the opposite configuration at *C*-2. Rationalization for the selectivity of the DIBAL reactions was described to derive from an intramolecular transfer of hydride from the reagent to the angular center before complete planarity of the iminium ion was realized. Lastly, hydrogenolytic cleavage of the benzyl moiety afforded chiral 2-substituted perhydroazepines in good yields, and good enantiomeric excesses (84–94%).

III. Experimental

General Methods: ^{1}H NMR spectra were recorded at 300 or 400 MHz and data were reported as follows: chemical shifts, in parts per million referenced to the internal chloroform ($CHCl_3$) peak (7.27 ppm), (multiplicity, coupling constant(s), number of protons). ^{13}C NMR spectra were recorded at 75 or 100 MHz, with chemical shifts referenced to the central peak of the $CDCl_3$ triplet (77.0 ppm). Fourier transform infrared absorption spectra were recorded on a Perkin–Elmer model PE 1600 spectrophotometer. Circular dichroism spectra were recorded on an Aviv 202 CD spectrometer at 25° C. Low resolution mass spectra (GC–MS) were obtained with a Hewlett–Packard model 5890 instrument equipped with a Hewlett–Packard 5970B mass selective detector (ionization potential 70 eV). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia. Optical rotations were determined with a Rudolph Research Autopol III instrument and were referenced to the sodium D line (598 nm). Melting points were measured in open Pyrex capillary tubes and are uncorrected. High performance liquid chromatography (HPLC) was performed with Regis Pirkle Covalent and Chiracel OD chiral columns. Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230–400 mesh), (60 Å). TLCs of compounds were visualized by UV light (254 nm), or by using potassium permanganate or vanillin stain.

All nonaqueous reactions were conducted under an argon atmosphere in a flame dried apparatus. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Concentrations were performed under reduced pressure with a rotary evaporator.

Solvents: Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. Dichloromethane, benzene, toluene, triethylamine, diisopropylamine, and acetonitrile were dried via distillation from calcium hydride and maintained under an inert atmosphere (Ar or N_2). Tetrahydrofuran and diethyl ether were dried via distillation from sodium benzophenone ketyl, and maintained under an inert atmosphere. Pyridine was distilled from calcium hydride and stored over 4 Å molecular sieves. Dimethylsulfide, packaged under nitrogen in 1 L Sure/Seal bottles, was purchased from Aldrich.

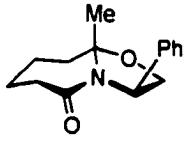
Compounds: (*R*)-Phenylglycinol was provided by The Upjohn Company. The synthesis of 8-methyl-6-oxononanoic acid was adapted from Koga.[15b] The following compounds were synthesized according to literature procedures: (*S*)-*tert*-leucinol,[21c] 6-oxooctanoic acid,[15a] benzo-fused keto acid **2.63**,[26] and (*S*)-*tert*-leucinol 5,5-lactam **2.70**.[1a] All other reagents were commercially available (Aldrich) and used without further purification.

Circular Dichroism Spectra: Spectra of solutions (2.0–0.2 mg/mL in acetonitrile) were measured from 300 to 190 nm, at 25 °C, in a 1 mL cuvette, for the purpose of making qualitative comparisons (positive or negative Cotton effects) among compounds. Molecular ellipticities were not recorded.

8-Methyl-6-oxononanoic Acid. Isovaleryl chloride (9.3 mL, 76.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise (addition funnel) over the course of 30 min to a solution of 1-morpholinocyclopentene (10.4 mL, 65.3 mmol) and Et_3N (10.9 mL, 78.4 mmol) in CH_2Cl_2 (35 mL) at 0 °C. This mixture was allowed to warm to room temperature and stirring was maintained for 4 d. Then, 6 M HCl (35 mL) was added, the mixture was

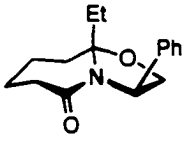
heated to reflux for 5 h, and then it was cooled to room temperature. The phases were separated, and the organic one was washed with brine (35 mL) and dried (Na_2SO_4).

The crude diketone was dissolved in water (15 mL), NaOH (9.0 g, 225 mmol) was added, and the solution was heated to reflux for 1 h. The mixture was poured into ice water (70 mL), acidified to pH 3 with conc. HCl, and extracted with CH_2Cl_2 (2 x 35 mL). The organic extracts were washed with brine (35 mL), dried (Na_2SO_4), and triturated with hexanes to provide 3.6 g (29%) of 8-methyl-6-oxononanoic acid as a light tan solid: mp = 37.5–39.5 °C. The aqueous material was further acidified to pH 2, saturated with solid NaCl, and extracted with EtOAc (2 x 100 mL). The organic phase was dried (Na_2SO_4) and concentrated to provide an additional 5.0 g (41%) of the keto acid as an impure oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, *J* = 6.5 Hz, 6H), 1.64 (apt s, 4H), 2.15 (*m*, 1H), 2.30 (d, *J* = 7.4 Hz, 2H), 2.39–2.43 (*m*, 4H), 11.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 22.8, 23.2, 24.4, 24.9, 34.0, 43.0, 52.1, 179.8, 210.7; IR (neat) 1698 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{10}H_{18}O_3$ $(M+H)^+$ 187.1334, found 187.1338. This material was used without further purification.



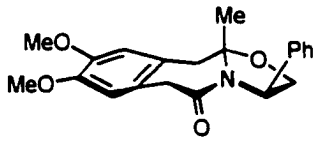
General Procedure for the Synthesis of 5,7-Bicyclic Lactams; Angular Methyl Lactam 2.48. 6-Oxoheptanoic acid (2.0 g, 13.7 mmol) and (*R*)-phenylglycinol (1.9 g, 13.7 mmol) were combined in 137 mL toluene and heated to reflux with azeotropic removal of water for 3 d, cooled, concentrated, and the residue dissolved in EtOAc (100 mL). This solution was washed with 2 M NaOH (25 mL), 1 M HCl (25 mL) and saturated (aqueous) $NaHCO_3$ (25 mL) and then dried ($MgSO_4$). Flash

chromatography of the residue (hexanes/EtOAc 2:1) provided 630 mg of *exo*-methyl **2.48** as a yellow oil that solidified upon standing (19%), 285 mg of *endo*-methyl **2.49** as a pale yellow solid (8%), and 61 mg (2%) of **2.48/2.49** as an epimeric mixture (1:1.4). **2.48**: mp = 96–98 °C; R_f = 0.21 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = –65.7 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66–2.11 (m, 9H), 2.57–2.68 (m, 2H), 4.03 (dd, *J* = 5.2 Hz and 9.0 Hz, 1H), 4.38 (dd, *J* = 7.0 Hz and 9.0 Hz, 1H), 5.33 (dd, *J* = 5.0 Hz and 6.9 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 24.4, 37.3, 39.7, 62.0, 70.3, 95.7, 126.6, 127.5, 128.7, 140.5, 171.39; IR (neat) 1643, 1403 cm^{-1}; MS *m/z* 245. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 7.79; N, 5.71. **2.49**: mp = 103–104 °C; R_f = 0.14 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = 1.14 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61–2.08 (m, 8H), 2.25–2.31 (m, 1H), 2.60–2.64 (m, 2H), 4.05 (dd, *J* = 1.5 Hz and 9.2 Hz, 1H), 4.41 (dd, *J* = 6.7 Hz and 9.0 Hz, 1H), 5.21 (br d, *J* = 6.1 Hz, 1H), 7.25–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 24.4, 24.9, 38.2, 40.1, 61.5, 70.3, 95.3, 126.8, 127.5, 128.7, 142.2, 171.0; IR (neat) 1629, 1412 cm^{-1}; MS *m/z* 245. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.37; H, 7.81; N, 5.74.



Angular Ethyl 5,7-Bicyclic Lactam 2.44. Synthesized from 6-oxooctanoic acid[15a] (500 mg, 3.16 mmol) and (*R*)-phenylglycinol (434 mg, 3.16 mmol) in 50 mL toluene using the general procedure. Flash chromatography of the residue (hexanes/EtOAc 5:2) provided 330 mg (40%) of **2.44** as an epimeric mixture (**2.44/2.45** 2.3:1). Recrystallization from Et_2O provided purified *endo*-ethyl **2.45**, as a 12:1 mixture, as long

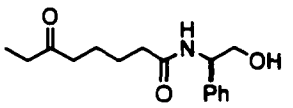
colorless needles. While under aspirator pressure during collection of **2.45**, *exo*-ethyl **2.44** precipitated from the mother liquor as a white solid, essentially free from the minor diastereomer. **2.44**: mp = 137–138 °C; R_f = 0.34 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = –49.5 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.63–2.04 (m, 6H), 2.13–2.31 (m, 2H), 2.48–2.67 (m, 2H), 3.94 (dd, *J* = 5.9 Hz and 9.0 Hz, 1H), 4.34 (dd, *J* = 7.2 Hz and 9.2 Hz, 1H), 5.29 (dd, *J* = 5.9 Hz and 7.2 Hz, 1H), 7.22–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 23.7, 24.2, 29.3, 35.3, 37.1, 61.7, 70.1, 98.0, 126.5, 127.4, 128.7, 140.3, 171.6; IR (neat) 1634 cm^{-1}; MS *m/z* 259. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.20; H, 8.10; N, 5.43. **2.45**: mp = 92–94 °C; R_f = 0.30 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = –4.67 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.50–1.67 (m, 2H), 1.74–2.09 (m, 4H), 2.26–2.35 (m, 2H), 2.50–2.54 (m, 2H), 3.88 (dd, *J* = 2.1 Hz and 9.1 Hz, 1H), 4.25 (dd, *J* = 6.9 Hz and 9.1 Hz, 1H), 5.19 (dd, *J* = 1.9 Hz and 6.7 Hz, 1H), 7.16–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 21.2, 24.3, 26.9, 35.8, 38.2, 61.6, 70.5, 97.6, 126.8, 127.4, 128.6, 142.2, 171.0; IR (neat) 1637 cm^{-1}; MS *m/z* 259. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.65; H, 8.19; N, 5.26.



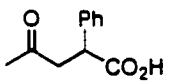
Benzo-fused 5,7-Bicyclic Lactam 2.64. Synthesized from benzo-fused keto acid **2.63**[26] (300 mg, 1.19 mmol) and (*R*)-phenylglycinol (163 mg, 1.19 mmol) in 50 mL toluene using the general procedure. Flash chromatography of the residue (hexanes/EtOAc 1:1) provided 166 mg (39%) of the *exo*-diastereomer **2.64** as a solid, and 109 mg (26%) of the *endo*-diastereomer **2.65**. **2.64**: mp = 138–139 °C; R_f = 0.19

(hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = –48.5 (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 3.17 (d, *J* = 14.8 Hz, 1H), 3.43 (d, *J* = 15.0 Hz, 1H), 3.80–3.93 (m, 9H), 4.47 (t, *J* = 8.7 Hz, 1H), 5.42 (apt t, 1H), 6.72 (s, 1H), 6.75 (s, 1H), 7.16–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 21.3, 25.4, 42.9, 43.8, 56.3, 60.9, 69.2, 94.6, 112.9, 113.7, 125.6, 125.8, 126.5, 127.3, 128.8, 140.6, 148.3, 167.4; IR (neat) 1639 cm^{-1}; MS *m/z* 353. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.68; H, 7.12; N, 3.60. **2.65**: mp = 147–148 °C; R_f = 0.11 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = +79.6 (c 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H), 3.29 (d, *J* = 15.4 Hz, 1H), 3.42 (d, *J* = 15.2 Hz, 1H), 3.50 (d, *J* = 15.5 Hz, 1H), 3.72–3.84 (m, 5H), 3.92 (s, 3H), 4.38 (dd, *J* = 7.4 Hz and 9.1 Hz, 1H), 4.99 (dd, *J* = 1.9 Hz and 7.4 Hz, 1H), 6.67 (s, 1H), 6.80–6.83 (m, 3H), 7.07–7.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 42.9, 44.4, 56.2, 56.3, 60.3, 70.6, 94.0, 112.8, 113.8, 125.7, 126.5, 127.2, 127.3, 128.4, 141.8, 148.1, 148.2, 167.4; IR (neat) 1652 cm^{-1}; MS *m/z* 353. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.17; H, 6.60; N, 3.95.

Methyl 6-Oxooctanoate. Thionyl chloride (0.25 mL, 3.48 mmol) was added dropwise to MeOH (2 mL) at –10 °C. After 10 min, 6-oxooctanoic acid[15a] (0.50 g, 3.16 mmol) was added as a solid in one portion. The mixture was stirred at room temperature for 2 h, concentrated, and the residue dissolved in 100 mL EtOAc. This solution was washed with saturated (aqueous) $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated to provide 540 mg of the ester as an orange oil (98%): R_f = 0.57 (hexanes/EtOAc 1:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.89 (m, 3H), 1.45 (m, 4H), 2.15 (m, 2H), 2.27 (m, 4H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.9, 23.3, 24.5, 33.9, 35.9, 41.9, 51.5, 173.9, 211.2; IR (neat) 1737, 1708, 1249, 1196, 1167 cm^{-1}; MS *m/z* 172. This material was used without further purification.



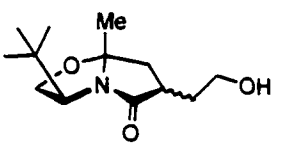
Keto Amide 2.60. Oxalyl chloride (0.34 mL, 4.11 mmol) was added dropwise to a 0 °C stirred solution of 6-oxooctanoic acid[15a] (500 mg, 3.16 mmol) in CH_2Cl_2 (40 mL), followed by 2 drops DMF. This was allowed to reach room temperature over 1 h, after which time the mixture was concentrated to dryness. The crude acid chloride was dissolved in CH_2Cl_2 (40 mL), Et_3N (1.1 mL. 7.9 mmol) and (*R*)-phenylglycinol (477 mg, 3.48 mmol) were added, and this mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by the addition of 1 M HCl (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The organic phases were combined and washed with saturated (aqueous) $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), and dried ($MgSO_4$). Recrystallization of this material from EtOAc provided 614 mg of **2.60** (70%): R_f = 0.27 (EtOAc); ^{1}H NMR (300 MHz) δ 1.07 (t, *J* = 7.4 Hz, 3H), 1.63 (m, 4H), 2.26 (apt t, 2H), 2.45 (m, 4H), 3.10–3.45 (br s, 1H), 3.86 (apt d, 2H), 5.08 (m, 1H), 6.68 (br d, 1H), 7.27–7.42 (m, 5H). This material was used without further purification.



1-Phenyl-4-oxopentanoic acid 2.75. Lithium diisopropylamide was generated as follows. *n*-Butyl lithium (13.4 mL, 2.5 M in hexanes) was added to a stirred solution of diisopropylamine (4.8 mL, 34.3 mmol) in THF (85 mL) at 0 °C. After 15 min, this solution was cooled to –78 °C. Phenylacetic acid (2.1 g, 15.3 mmol) was added as a solution in THF (10 mL), the mixture was warmed to 0 °C and stirred for 10 min, and then re-cooled to –78 °C. 3-Iodo-2-methylpropene (4.2 g, 22.9 mmol), prepared by

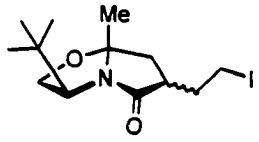
Finkelstein reaction (NaI in acetone) of 3-chloro-2-methylpropene, was added neat, and the mixture was stirred at –78 °C for 1 h. The reaction was quenched by the addition of water (5 mL), the mixture was concentrated, and the residue was partitioned between Et_2O (80 mL) and water (80 mL). The phases were separated and the aqueous one was acidified to pH 2 with 6 M HCl. The aqueous phase was then extracted with Et_2O (2 x 40 mL), and the combined organic phases (80 mL total) were then washed with brine (2 x 50 mL), and dried ($MgSO_4$), to provide 2.8 g (96%) of a crude orange oil that was used without purification in the next step.

To a stirred solution of the olefin (2.8 g, 14.7 mmol) in EtOAc (184 mL) at –78 °C was introduced ozone (O_2 passed through an ozone generator at 6 psi and 80 volts) via gas dispersion tube until the solution turned blue. Dimethyl sulfide (5.4 mL, 73.5 mmol) was added, the mixture was allowed to reach room temperature, and then it was concentrated. The residue was dissolved in 5% aqueous NaOH (60 mL) and washed with Et_2O (2 x 50 mL). The aqueous phase was acidified to pH 2 with concentrated HCl (exotherm) and extracted with Et_2O (2 x 50 mL). These ethereal extracts were dried ($MgSO_4$) and concentrated to provide 2.3 g of keto acid **2.75** as a colorless oil: ^{1}H NMR (300 MHz) δ 2.21 (s, 3H), 2.78 (dd, J = 4.0 Hz and 17.7 Hz, 1H), 3.40 (dd, J = 10.3 Hz and 18.1 Hz, 1H), 4.15 (dd, J = 4.6 Hz and 10.2 Hz, 1H), 7.32–7.82 (m, 5H). This material was used without purification in the next step.



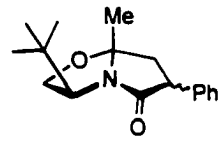
α-(2-Hydroxyethyl) Bicyclic Lactam 2.71. LDA was generated as described in the synthesis of compound **2.75**. To a solution of LDA (4.46 mmol) in 7 mL

THF/hexanes (5:2) at –78 °C was added lactam **2.70** (800 mg, 4.06 mmol) as a solution in THF (4 mL). After 30 min, a 2 M solution of ethylene oxide (0.3 mL/6.08 mmol of ethylene oxide was condensed at -78 °C and then diluted with 3 mL THF) was added via cannula. The reaction was warmed to –20 °C and stirring continued for 20 h. Saturated (aqueous) NH_4Cl (10 mL) was added, the mixture was diluted with 40 mL hexane/Et_2O (1:1), and the phases were separated. The organic phase was washed with brine (2 x 10 mL), and dried ($MgSO_4$). Flash chromatography of the residue (hexanes/EtOAc 2:1) provided 467 mg (48%) of lactam **2.71** as an epimeric mixture, and 209 mg (26%) of starting lactam **2.70**: ^{1}H NMR (300 MHz) δ 0.92 (s, 9H), 1.49 (s, 3H), 1.56–1.66 (m, 1H), 1.84–2.03 (m, 2H), 2.41 (dd, *J* = 8.2 Hz and 12.4 Hz, 1H), 2.99–3.10 (m, 1H), 3.60–3.80 (m, 4H), 3.93 (apt t, 1H), 4.15 (dd, *J* = 8.0 Hz and 9.3 Hz, 1H); ^{13}C NMR (100 MHz) δ 24.5, 27.2, 33.2, 33.4, 43.5, 43.6, 61.1, 64.6, 68.5, 98.4, 181.5; MS *m/z* 241; HRMS (FAB$^+$) calcd for $C_{13}H_{23}NO_3$ $(M+H)^+$ 242.1756, found 242.1748.

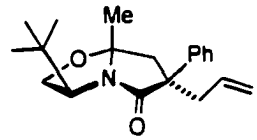


α-(2-Iodoethyl) Bicyclic Lactam 2.72. To a stirred solution of hydroxylactam **2.71** (87 mg, 0.36 mmol) in 1.0 mL CH_3CN/Et_2O (2:3) at 0 °C was added PPh_3 (123 mg, 0.47 mmol), imidazole (34 mg, 0.49 mmol), and I_2 (131 mg, 0.52 mmol). After 1 h, the reaction mixture was diluted with Et_2O (60 mL) and sequentially washed with saturated (aqueous) $Na_2S_2O_3$, saturated (aqueous) $CuSO_4$, and H_2O. The organic phase was dried briefly ($MgSO_4$). Flash chromatography of the residue (hexanes) provided 92 mg (73%) of **2.72**: ^{1}H NMR (300 MHz) δ 0.94 (s, 9H), 1.51 (s, 3H), 1.61–1.83 (m, 2H), 2.31–

2.51 (m, 2H), 2.99–3.10 (m, 1H), 3.19–3.29 (m, 1H), 3.35–3.47 (m, 1H), 3.65–3.75 (m, 1H), 3.90–3.99 (m, 1H), 4.12–4.22 (m, 1H); ^{13}C NMR (100 MHz) δ 4.6, 24.9, 27.3, 33.4, 34.5, 42.7, 45.0, 64.9, 68.7, 98.2, 180.1; MS *m/z* 351; HRMS (FAB$^+$) *calcd for* $C_{19}H_{22}INO_2$ $(M+H)^+$ 352.0774, found 352.0782.

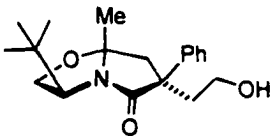


α-Phenyl Bicyclic Lactam 2.76. Prepared from 1-phenyl-4-oxopentanoic acid (**2.75**) (2.3 g, 11.9 mmol) and (*S*)-*tert*-leucinol[21c] (1.40 g, 11.9 mmol) in 50 mL toluene using the general procedure described for the synthesis of 5,7-bicyclic lactams. Flash chromatography (hexanes/EtOAc 6:1) provided 2.5 g (78%) of **2.76** as a white waxy solid: ^{1}H NMR (300 MHz) δ 1.02 (s, 4H), 1.05 (s, 5H), 1.47 (s, 1.6H), 1.65 (s, 1.4H), 2.31–2.51 (m, 1H), 2.68–2.84 (m, 1H), 3.82–4.31 (m, 4H), 7.21–7.52 (m, 5H). This material was used without purification in the next step.



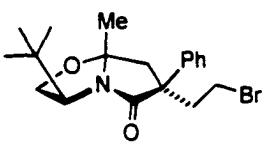
(*S*)-α-Allyl-α-phenyl Bicyclic Lactam 2.77. LDA was generated as described in the synthesis of compound **2.75**. Lactam **2.76** (1.5 g, 5.49 mmol) was added as a solution in THF (5 mL) over the course of 5 min to a solution of LDA (12.0 mmol) in 44.8 mL THF/hexanes (8.3:1) at –78 °C, and the mixture was stirred for 45 min. Allyl bromide (0.95 mL, 11.0 mmol) was added dropwise, and the mixture was stirred at –78 °C for 1 h. The reaction was quenched with H_2O (2 mL), the mixture was concentrated, and the residue was partitioned between Et_2O (50 mL) and saturated (aqueous) NH_4Cl

(30 mL). The phases were separated and the organic one was washed with saturated (aqueous) $NaHCO_3$ (30 mL) and brine (30 mL), and then dried ($MgSO_4$). Flash chromatography of the residue (hexanes/EtOAc 6:1) provided 0.98 g (57%) of pure **2.77**, and 0.65 g (38%) as a mixture of epimers (1:1): R_f = 0.37 (hexanes/EtOAc 1:1); ^1H NMR (300 MHz) δ 1.00 (s, 9H), 1.19 (s, 3H), 2.46–2.85 (m, 4H), 3.79–4.01 (m, 2H), 4.15–4.28 (m, 1H), 4.99–5.15 (m, 2H), 5.62–5.76 (m, 1H), 7.19–7.51 (m, 5H). This material was used without further purification in the next step.

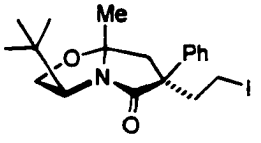


α-(2-Hydroxyethyl)-α-phenyl Bicyclic Lactam 2.78. To lactam **2.77** (500 mg, 1.60 mmol) in 20 mL THF/H_2O (3:1) at 0 °C was added *t*-butyl alcohol (2 mL), OsO_4 (20 mg, 0.08 mmol) and NMO (374 mg, 3.19 mmol), and the mixture was warmed to room temperature with stirring overnight. Sodium bisulfate (1.6 g) was added and the mixture was stirred for 15 min, then it was concentrated. The residue was partitioned between H_2O (40 mL) and EtOAc (50 mL), the phases were separated, and the organic one was washed with brine, and then dried (Na_2SO_4). The crude diol was re-dissolved in 20 mL THF/H_2O (3:1), and $NaIO_4$ (682 mg, 3.19 mmol) was added. After stirring at room temperature for 4.5 h, the mixture was concentrated and the residue was partitioned between Et_2O (75 mL) and brine (30 mL). The phases were separated and the ethereal one was washed with brine (30 mL), and dried (Na_2SO_4). $NaBH_4$ (91 mg, 2.39 mmol) was added to the crude aldehyde dissolved in EtOH (16 mL). The reduction was quenched after 20 min by the careful addition of 1 M HCl (10 mL), and the mixture was concentrated. EtOAc (20 mL) was added, the phases were separated, and the aqueous

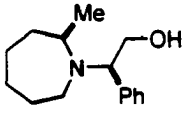
one was extracted with EtOAc (20 mL). The combined organic phases were washed with H_2O and brine, and dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 1:1) provided 335 mg (70%) of **2.78** as a colorless oil: R_f = 0.24 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz) δ 0.99 (s, 9H), 1.09 (s, 3H) 1.98–2.07 (m, 1H), 2.13–2.23 (m, 1H), 2.48 (d, J = 12.8 Hz, 1H), 2.76 (d, J = 12.6 Hz, 1H), 3.25–3.33 (m, 1H), 3.43–3.49 (m, 1H), 3.84–3.97 (m, 2H), 4.25 (apt t, 1H), 4.39 (br s, 1H), 7.26–7.44 (m, 5H); ^{13}C NMR (75 MHz) δ 24.7, 27.5, 33.5, 42.6, 51.5, 58.8, 64.7, 68.6, 98.1, 126.5, 127.2, 129.0, 142.0, 182.2; IR (neat) 3402, 1704 cm^{-1}; MS *m/z* 317; HRMS (FAB$^+$) calcd for $C_{19}H_{27}NO_3$ $(M+H)^+$ 318.2069, found 318.2073.



α-(2-Bromoethyl)-α-phenyl Bicyclic Lactam 2.79a. To a stirred solution of lactam **2.78** (103 mg, 0.32 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C was added PPh_3 (124 mg, 0.47 mmol) and NBS (84 mg, 0.47 mmol). After 1.5 h, H_2O was added and the reaction mixture was diluted with additional CH_2Cl_2. The phases were separated and the organic one was washed with brine, and dried ($MgSO_4$). Flash chromatography of the residue (hexanes/ether 9:1) provided 120 mg (100%) of **2.79a** as a colorless oil: R_f = 0.72 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz) δ 0.98 (s, 9H), 1.13 (s, 3H), 2.29–2.55 (m, 3H), 2.81 (d, J = 12.8 Hz, 1H), 2.91–3.00 (m, 1H), 3.61–3.69 (m, 1H), 3.82–3.96 (m, 2H), 4.24 (apt t, 1H), 7.29–7.43 (m, 5H); MS *m/z* 379 (M-1), 381 (M+1). This material was used without further purification.

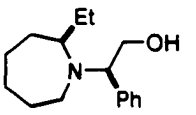


α-(2-Iodoethyl)-α-phenyl Bicyclic Lactam 2.79b. To a stirred solution of lactam **2.78** (60 mg, 0.19 mmol) in 1.0 mL CH_3CN/Et_2O (2:3) at 0 °C was added PPh_3 (64 mg, 0.25 mmol), imidazole (18 mg, 0.26 mmol), and I_2 (69 mg, 0.27 mmol). After 1 h, the reaction mixture was diluted with Et_2O (10 mL) and sequentially washed with saturated (aqueous) $Na_2S_2O_3$, saturated (aqueous) $CuSO_4$, and H_2O. The organic phase was dried briefly ($MgSO_4$). Flash chromatography of the residue (hexanes, then hexanes/EtOAc 9:1) provided 69 mg (85%) of **2.79b** as a yellow solid: mp = 94–96 °C; R_f = 0.61 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz) δ 1.00 (s, 9H), 1.14 (s, 3H), 2.38–2.59 (m, 3H), 2.71–2.80 (m, 2H), 3.39–3.48 (m, 1H), 3.83–3.97 (m, 2H), 4.25 (apt t, 1H), 7.30–7.44 (m, 5H); ^{13}C NMR (100 MHz) δ -0.1, 25.0, 27.4, 33.4, 45.2, 49.3, 59.2, 64.8, 68.5, 97.5, 126.4, 127.5, 129.2, 141.2, 180.5; MS *m/z* 427; HRMS (FAB$^+$) calcd for $C_{19}H_{26}INO_2$ $(M+H)^+$ 428.1087, found 428.1094.



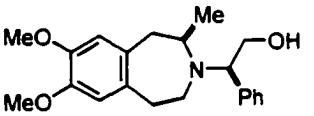
***N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*R*)-methyl-hexahydrozepine 2.93.** Alane was generated as follows. THF (4 mL) was added slowly to $AlCl_3$ (48 mg, 0.36 mmol) at 0 °C. After stirring 5 minutes, a solution of $LiAlH_4$ (41 mg, 1.07 mmol) in 1 mL THF was added slowly via syringe. The mixture was stirred at room temperature for 20 min and then cooled to –78 °C. To the alane solution was added a precooled (–78 °C) solution of lactam **2.48** (73 mg, 0.30 mmol) in 3 mL THF via cannula. After 45 min, the reaction was warmed to room temperature, stirred an additional 1 h, and then re-cooled to 0 °C.

The reaction was quenched by the careful addition of 1 M HCl (5 mL), the phases were separated, and the aqueous one was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were washed with 2 M NaOH (10 mL, which was back extracted with 10 mL CH_2Cl_2) and brine (10 mL), and then dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 76 mg (80%) of **2.93** that remained a little impure. **2.93** was shown to be a mixture of diastereomers (22.0:1) by HPLC analysis of derivative **(–)-2.97d**: ^{1}H NMR (300 MHz) δ 1.17 (d, *J* = 6.3 Hz, 3H), 1.30–1.46 (m, 2H), 1.56–1.74 (m, 6H), 2.42–2.50 (m, 1H), 2.87–2.95 (m, 1H), 3.16–3.22 (m, 1H), 3.38 (br s, 1H), 3.69 (dd, *J* = 5.2 Hz and 10.3 Hz, 1H), 3.92 (apt t, 1H), 4.06 (dd, *J* = 5.0 Hz and 10.3 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 20.5, 23.7, 29.3, 31.7, 35.6, 44.9, 54.1, 61.0, 65.0, 127.8, 128.5, 128.8, 138.3; MS *m/z* 233; HRMS (FAB$^+$) calcd for $C_{15}H_{23}NO$ $(M+H)^+$ 234.1858, found 234.1856. This material was used without further purification in the next step.



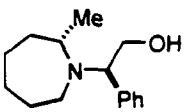
***N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*R*)-ethyl-hexahydrozepine 2.98.** Alane was prepared as described for compound **2.93**. To a solution of alane (0.43 mmol) in THF (5.2 mL) at –78 °C was added lactam **2.44** (92 mg, 0.35 mmol) as a solution in THF (3.5 mL). This mixture was stirred for 1 h, warmed to –40 °C and stirred for 14 h, and then warmed to –20 °C and stirred for an additional 4 h. The reaction was quenched by the careful addition of 1 M HCl (3 mL), brine (1 mL) was added, the phases were separated, and the aqueous one was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were washed with 1 M NaOH (10 mL, back extracted with 10 mL CH_2Cl_2) and brine (10 mL), and then dried (Na_2SO_4). Flash chromatography

of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 59 mg (68%) of **2.98** that remains a little impure. **2.98 was shown to be a mixture of diastereomers** (11.5:1) by HPLC analysis of derivative **2.101b**: ^{1}H NMR (300 MHz) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.31–1.81 (m, 10H), 2.49–2.57 (m, 1H), 2.86–2.93 (m, 2H), 3.45 (br s, 1H), 3.68 (dd, *J* = 5.0 Hz and 10.1 Hz, 1H), 3.93 (apt t, 1H), 4.04 (dd, *J* = 5.0 Hz and 10.1 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 11.4, 23.9, 26.4, 29.4, 30.3, 31.1, 45.1, 61.0, 61.1, 65.8, 127.8, 128.4, 128.8, 138.4; MS *m/z* 247; HRMS (FAB$^+$) calcd for $C_{16}H_{25}NO$ $(M+H)^+$ 248.2014, found 248.2021. This material was used without further purification in the next step.



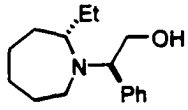
***N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*R*)-methyl-benzazepine 2.103.** To a stirred solution of lactam **2.64** (70 mg, 0.20 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (27 mg, 0.71 mmol) as a solid in one portion. The heterogeneous mixture was allowed to reach room temperature, was stirred for 29 h, and then was heated to reflux for 15 min. The mixture was then cooled to 0 °C, quenched by the careful addition of 1 M HCl (3.0 mL), and then made alkaline (pH 11) by the addition of 2 M NaOH. The phases were separated and the aqueous one was extracted with EtOAc (4 x 10 mL). The combined organic phases were washed with 1 M NaOH (10 mL, which was back extracted with 10 mL of EtOAc) and brine (10 mL), and dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 34 mg (50%) of **2.103** as an oil and a 20:1 mixture of diastereomers: ^{1}H NMR (400 MHz) δ 0.78 (d, *J* = 6.1 Hz, 3H), 2.56 (dd, *J* = 6.1 Hz and 15.0 Hz, 1H), 2.64 (dd, *J* = 7.0 Hz and 14.0 Hz, 1H), 2.68–2.76 (m, 1H), 2.89 (br dd, *J* = 8.7 Hz and 14.0 Hz, 1H), 3.01 (br dd, *J* =

9.3 Hz and 11.0 Hz, 1H), 3.10 (apt d, J = 13.9 Hz, 1H), 3.17 (apt t, J = 5.5 Hz, 1H), 3.73 (dd, J = 5.1 Hz and 10.5 Hz, 1H), 3.80 (s, 6H), 3.90 (apt t, J = 9.2 Hz, 1H), 3.99 (dd, J = 4.7 Hz and 7.7 Hz, 1H), 6.51 (s, 1H), 6.55 (s, 1H), 7.24–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 16.3, 36.9, 43.2, 45.8, 52.2, 56.2, 56.3, 61.4, 66.9, 112.9, 114.2, 128.0, 128.5, 128.7, 131.0, 133.3, 139.3, 147.0, 147.2; HRMS (FAB$^+$) calcd for $C_{21}H_{27}NO_3$ $(M+H)^+$ 342.2069, found 342.2071. This material was used without further purification in the next step.

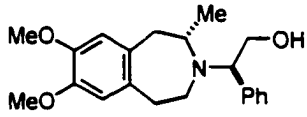


General Procedure for the Reduction of *endo*-Bicyclic Lactams with DIBAL; *N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*S*)-methyl-hexahydroazepine 2.94. To a solution of *endo*-bicyclic lactam **2.49** (82 mg, 0.33 mmol) in THF (5 mL) at –78 °C was added diisobutylaluminum hydride (0.60 mL, 3.34 mmol) dropwise. The solution was stirred, with gradual warming to room temperature, for 12 h. The mixture was then cooled to 0 °C and quenched by the careful addition of 1 M HCl (5.0 mL). It was then made alkaline (pH 11) by the addition of 2 M NaOH, and stirred for 0.5 h with warming to room temperature. The phases were separated and the aqueous one was extracted with EtOAc (5 x 10 mL). The combined organic phases were washed with 1 M NaOH (10 mL, which was back extracted with 10 mL EtOAc) and brine (10 mL), and dried (Na_2SO_4). The crude residue was purified by chromatography (hexanes/EtOAc 10:1, then EtOAc), to provide 73 mg (95 %) of amino alcohol **2.94** that remains a little impure. **2.94** was shown to be a mixture of diastereomers (21.2:1) by HPLC analysis of derivative **(+)-2.97d**: ^{1}H NMR (300 MHz) δ 1.00 (d, J = 6.4 Hz, 3H), 1.26–1.50 (m, 4H), 1.51–1.80 (m, 4H), 2.52–3.08 (bs, 1H), 2.76–2.89 (m, 2H), 3.17–3.30 (m, 1H), 3.78 (apt

t, J = 6.2 Hz, 2H), 3.95 (dd, J = 8.1 Hz and 14.6 Hz, 1H), 7.26–7.38 (m, 5H). This material was used without further purification in the next step.

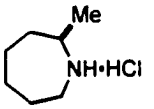


***N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*S*)-ethyl-hexahydroazepine 2.99.** Prepared from lactam **2.45** (47 mg, 0.18 mmol) using the general procedure for DIBAL reduction. Flash chromatography of the crude product (hexanes/EtOAc 10:1, then EtOAc) provided 27 mg (61%) of **2.99** that remains a little impure. Amino alcohol **2.99** was shown to be a mixture of diastereomers (30.5:1) by HPLC analysis of derivative **2.102b**: ^{1}H NMR (300 MHz) δ 0.84 (t, J = 7.4 Hz, 3H), 1.30–1.81 (m, 10H), 2.78–2.95 (m, 3H), 3.70–3.85 (m, 2H), 4.0 (apt t, J = 6.8 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}C NMR (100 MHz) δ 11.6, 24.3, 26.3, 29.2, 29.6, 32.9, 45.2, 61.7, 62.7, 68.6, 127.6, 128.5, 128.9, 140.7; MS *m/z* 247; HRMS (FAB$^+$) calcd for $C_{16}H_{25}NO$ $(M+H)^+$ 248.2014, found 248.2013. This material was used without further purification in the next step.

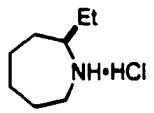


***N*-(1'-(*R*)-Phenyl-2'-hydroxy-ethyl)-2-(*S*)-methyl-benzazepine 2.104.** Prepared from lactam **2.65** (77 mg, 0.22 mmol) using the general procedure for DIBAL reduction. Flash chromatography of the crude product (hexanes/EtOAc 10:1, then 1:1) provided 40 mg (53%) of **2.104** as an oil and a 30:1 mixture of diastereomers: ^{1}H NMR (300 MHz) δ 0.72 (d, J = 6.6 Hz, 3H), 2.56 (dd, J = 6.6 Hz and 14.7 Hz, 1H), 2.63–2.77 (m, 2H), 2.98–3.10 (m, 2H), 3.32 (apt d, J = 14.9 Hz, 1H), 3.37–3.44 (m, 1H), 3.68 (dd, J = 5.1

Hz and 10.9 Hz, 1H), 3.83–3.90 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.99 (dd, J = 5.2 Hz and 8.2 Hz, 1H), 6.59 (s, 1H), 6.64 (s, 1H), 7.31–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 13.9, 37.0, 42.4, 43.2, 55.2, 56.2, 56.3, 62.1, 70.3, 113.0, 114.3, 127.9, 128.7, 129.0, 131.0, 133.5, 140.1, 147.0, 147.1; MS *m/z* 341; HRMS (FAB$^+$) calcd for $C_{21}H_{27}NO_3$ $(M+H)^+$ 342.2069, found 342.2078. This material was used without further purification in the next step.

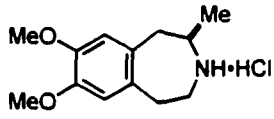


General Procedure for Hydrogenolysis of the Phenethyl Moiety; 2-(*R*)-Methyl-hexahydroazepine Hydrochloride (–)-2.96. A solution of amino alcohol **2.93** (25 mg, 0.11 mmol) in EtOH (2 mL) was hydrogenated over 5 mg of $Pd(OH)_2$. After 4 h, the mixture was filtered over Celite, and the pad was rinsed with Et_2O. Concentrated HCl (5 drops) was added to the filtrate prior to concentration. The crude solid was triturated with Et_2O (3 x 5 mL) to provide 13 mg (85%) of **(–)-2.96** as a white solid that was used without further purification: $[\alpha]^{23}_D$ = –1.8 (c 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 1.56 (d, J = 6.4 Hz, 3H), 1.63–2.13 (m, 8H), 3.18 (br s, 1H), 3.31 (br s, 1H), 3.43 (br s, 1H), 9.30 (br s, 1H), 9.65 (br s, 1H); ^{13}C NMR (100 MHz) δ 20.6, 25.0, 25.2, 27.0, 33.8, 44.9, 55.1.

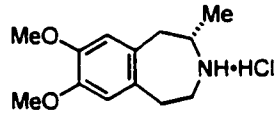


2-(*R*)-Ethyl-hexahydroazepine Hydrochloride (–)-2.100. Prepared from **2.98** (37 mg, 0.15 mmol) in 86% yield using the general procedure for hydrogenolysis: $[\alpha]^{23}_D$

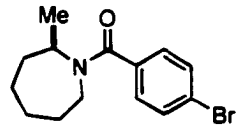
= –5.8 (c 1.0, CH_2Cl_2); ^1H NMR (300 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.55–2.13 (m, 10H), 3.17 (m, 2H), 3.31 (br s, 1H), 9.26 (br s, 1H), 9.57 (br s, 1H); ^{13}C NMR (100 MHz) δ 10.7, 25.1, 25.2, 27.2, 27.2, 30.3, 45.3, 60.5. This material was used without further purification in the next step.



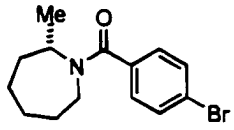
2-(*R*)-Methyl-benzazepine Hydrochloride (+)-2.105. Prepared from **2.103** (15 mg, 0.04 mmol) in 78% yield using the general procedure for hydrogenolysis: $[\alpha]^{23}_D$ = +0.42 (c 0.8, CH_2Cl_2); ^1H NMR (300 MHz) δ 1.49 (d, *J* = 6.0 Hz, 3H), 3.03 (br s, 3H), 3.20-3.30 (m, 2H), 3.44 (br s, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 6.59 (s, 1H), 6.62 (s, 1H), 9.89 (br d, 2H); ^{13}C NMR (100 MHz) δ 18.7, 32.4, 39.9, 44.5, 53.6, 56.3, 113.2, 113.9, 129.3, 131.2, 147.8, 147.9. Anal. Calcd for $C_{13}H_{20}ClNO_2$: C, 60.58; H, 7.82; N, 5.43. Found: C, 58.66; H, 7.55; N, 5.03.



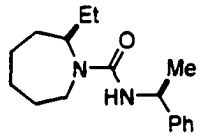
2-(*S*)-Methyl-benzazepine Hydrochloride (–)-2.105. Prepared from **2.104** (40 mg, 0.15 mmol) in 65% yield using the general procedure for hydrogenolysis: $[\alpha]^{23}_D$ = – 4.7 (c 1.3, CH_2Cl_2).



***N*-(*para*-Bromobenzoyl)-2-(*R*)-methyl-hexahydroazepine (–)-2.97d.** To a solution of 4-bromobenzoyl chloride (29 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added azepine hydrochloride **(–)-2.96** (13 mg, 0.09 mmol) as a solution in CH_2Cl_2 (5 mL), and 2 M NaOH (2 mL), dropwise. The mixture was stirred vigorously for 4 h with gradual warming to room temperature. The phases were separated and the aqueous one was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were washed with brine (2 mL), and dried (Na_2SO_4). The crude material was purified twice by flash chromatography (hexanes, then hexanes/EtOAc 10:1) to provide 16 mg (60%) of **(–)-2.97d** as a mixture of rotamers. HPLC analysis ((*R*,*R*) Whelk-02 Pirkle Covalent, hexanes/isopropanol 90:10, 1 mL/min) showed **(–)-2.97d** to be a 20.0:1 mixture of enantiomers, with the major one eluting second: $[\alpha]^{23}_D$ = –38.4 (c 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 1.02 (d, *J* = 6.9 Hz, 2H), 1.15–1.40 (m, 5H), 1.52–1.60 (m, 0.4H), 1.71–1.98 (m, 4H), 2.03–2.13 (m, 0.4 H), 2.73–2.92 (m, 0.6 H), 2.99 (dd, *J* = 11.8 Hz and 14.9 Hz, 0.4H), 3.40 (br d, *J* = 15.0 Hz, 0.4H), 3.55–3.67 (m, 0.6H), 4.21 (br d, *J* = 13.1 Hz, 0.6 H), 4.62–4.66 (m, 0.4 H), 7.17–7.24 (m, 2H), 7.50–7.53 (m, 2H); ^{13}C NMR (75 MHz) δ 19.6, 21.0, 25.0, 25.3, 27.0, 29.1, 31.1, 30.8, 35.3, 36.3, 40.0, 43.4, 50.4, 53.6, 122.7, 127.6, 127.7, 131.6, 131.7, 136.6, 136.8, 170.0; IR (neat) 1628, 1589, 1422 cm^{-1}; MS *m/z* 295 (M-1), 297 (M+1); HRMS (FAB$^+$) calcd for $C_{14}H_{18}{}^{79}BrNO$ $(M+H)^+$ 296.0650, found 296.0637.

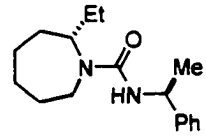


***N*-(*para*-Bromobenzoyl)-2-(*S*)-methyl-hexahydroazepine (+)-2.97d.** Prepared from **2.94** (after hydrogenolysis) as described for compound **(–)-2.97d**. HPLC analysis ((*R*,*R*) Whelk-02 Pirkle Covalent, hexanes/isopropanol 90:10, 1 mL/min) showed **(+)-2.97d** to be a 21.2:1 mixture of enantiomers: $[\alpha]^{23}_{D}$ = +29.8 (c 1.1, CH_2Cl_2).

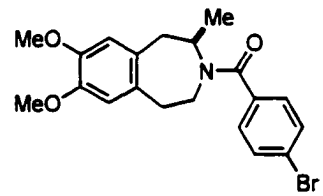


***N*-(1'-(*S*)-Methyl-benzylamino-carbonyl)-2-(*R*)-ethyl-hexahydroazepine 2.101b.** Azepine salt **(–)-2.100** (20 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (5 mL), washed with 2 M NaOH (2.5 mL, which was back extracted with 2 mL CH_2Cl_2), and dried (Na_2SO_4). The filtered solution was cooled to 0 °C and (*S*)-α-methylbenzyl isocyanate (0.03 mL, 0.21 mmol) was added. The mixture was stirred for 6 h with gradual warming to room temperature and was quenched with brine (5 mL). The phases were separated and the aqueous one was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried (Na_2SO_4) and the crude solid was purified by flash chromatography (hexanes, then hexanes/EtOAc 10:1) to provide 21 mg (64%) of **2.101b** as an off-white waxy solid. HPLC analysis (Chiracel OD, hexanes/isopropanol 97.5:2.5, 1 mL/min) showed **2.101b** to be an 11.5:1 mixture of diastereomers: mp = 72–75° C; $[\alpha]^{23}_{D}$ = –17.4 (c 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.15–1.36 (m, 4H), 1.40–1.66 (m, 4H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.66–1.92 (m, 4H), 2.09–2.19 (m, 1H), 2.82–2.97 (m, 1H), 3.53 (br s, 1H), 4.01 (br s, 1H), 4.64 (br d, *J* = 6.3 Hz, 1H), 5.10 (quintet, *J* = 7.0 Hz, 1), 7.26–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ

11.0, 14.3, 23.1, 25.0, 28.1, 28.9, 30.1, 34.4, 41.4, 50.2, 126.2, 127.1, 128.7, 145.2, 157.4; IR (neat) 3344, 1617, 1528, 1494 cm^{-1}; MS *m/z* 274; HRMS (FAB^+) calcd for $C_{17}H_{26}N_2O$ $(M+H)^+$ 275.2123, found 275.2120.



***N*-(1'-(*S*)-Methyl-benzylamino-carbonyl)-2-(*S*)-ethyl-hexahydroazepine 2.102b.** Prepared from **2.99** (after hydrogenolysis) in 50% yield (two steps) as described for compound **2.101b**. HPLC analysis (Chiracel OD, hexanes/isopropanol 97.5:2.5, 1 mL/min) showed **2.102b** to be a 30.5:1 mixture of diastereomers: mp = 97–102° C; $[\alpha]^{23}_D$ = +30.8 (c 0.5, CH_2Cl_2); ^1H NMR (400 MHz) δ 0.84 (t, *J* = 6.8 Hz, 3H), 1.16–1.82 (m, 12H), 1.46 (d, *J* = 6.8 Hz, 3H), 2.08 (m, 1H), 2.82 (m, 1H), 4.52 (br d, 1H), 5.05 (m, 1H), 7.19–7.34 (m, 5H); ^{13}C NMR (100 MHz) δ 11.1, 14.4, 23.0, 25.1, 28.2, 28.9, 30.1, 34.6, 41.4, 50.0, 126.3, 127.2, 128.8, 145.2, 157.4; IR (neat) 3333, 1622, 1528, 1494 cm^{-1}; MS *m/z* 274; HRMS (FAB^+) calcd for $C_{17}H_{26}N_2O$ $(M+H)^+$ 275.2123, found 275.2120.



***N*-(*para*-Bromobenzoyl)-2-(*R*)-methyl-benzazepine (–)-2.106.** Prepared from **(+)-2.105** (8 mg, 0.02 mmol) in 33% yield, as a mixture of rotamers, as described for compound **(–)-2.97d**: $[\alpha]^{23}_D$ = –38.4 (c 1.6, CH_2Cl_2); ^1H NMR (400 MHz) δ 1.06–1.50 (br d, 3H), 2.65–3.12 (m, 4.6H), 3.24 (br t, 0.4H), 3.61 (br d, 0.4H), 3.81 (s, 2.4H), 3.86 (s,

3.6H), 3.96 (br s, 0.6H), 4.62 (br d, 0.6H), 5.14 (br s, 0.4H), 6.49 (s, 0.6H), 6.57 (s, 0.4H), 6.64 (s, 0.4H), 6.69 (s, 0.6H), 6.99 (d, J = 6.8 Hz, 1.2H), 7.18 (d, J = 7.2 Hz, 0.8H), 7.47 (d, J = 7.6 Hz, 1.2H), 7.52 (d, J = 7.6 Hz, 0.8H); ^{13}C NMR (100 MHz) δ 16.4, 17.6, 30.0, 35.0, 36.5, 37.4, 41.3, 41.7, 43.1, 46.9, 53.3, 56.2, 56.4, 113.3, 113.6, 114.0, 114.4, 123.5, 128.1, 128.6, 128.8, 132.0, 136.2, 147.8, 170.7; IR (neat) 1628, 1518, 1429 cm^{-1}; HRMS (FAB^{+}) calcd for $C_{20}H_{22}{}^{79}BrNO_3$ $(M+H)^{+}$ 404.0861, found 404.0852.

IV. References

1 The extensive chemistry of the 5,5- and 5,6-bicyclic lactam systems has been thoroughly reviewed: a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503-69. b) Meyers, A. I. In *Stereocontrolled Organic Synthesis*; Trost, B. M. Ed.; Blackwell Scientific Publications: Cambridge, MA, 1994, 145-161. c) Meyers, A. I.; Brengel, G. P. *Chem. Comm.* **1997**, 1-8. d) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931-52. e) Groaning, M. D.; Meyers, A. I. *Tetrahedron*, in preparation.

2 a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36-42. b) Andres, C. J.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 3491-4. c) Andres, C. J.; Lee, P. H.; Nguyen, T. H.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 3189-93. d) Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. *J. Org. Chem.* **1995**, *60*, 4359-62. e) Meyers, A. I.; Fray, A. H. *Bull. Soc. Chim. Fr.* **1997**, *134*, 283-98. f) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 4639-42. g) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086-7. h) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399-400. i) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607-10.

3 a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294-6. b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858-9. c) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656-62. d) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084-5.

4 a) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum. L. J. *J. Org. Chem.* **1989**, *54*, 4243-6. b) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223-6. c) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074-84. The following reference describes the successful use of a γ-formyl acid in the preparation of a 5,5-bicyclic lactam: d) Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265-6. e) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493-5. f) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605-11.

5 a) Andres, C. J.; Spetseris, N.; Norton, J. R.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 1613-6. b) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry.* **1996**, *7*, 2501-4. c) Newhouse, B. J.; Meyers, A. I.; Sirisoma, N. S.; Braun, M.; Johnson, C. R. *Synlett* **1993**, 573-6.

6 Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051-4.

7 a) Kasparek, S. *Advanced Heterocyclic Chemistry* **1974**, *17*, 45-98. b) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341-2. c) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513-8. d) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657.

8 Hansen, D. W. Jr.; et al. *J. Med. Chem.* **1998**, *41*, 1361-1366.

9 a) Miyabe, H.; Torieda, H.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397-407. b) Herdeis, C.; Mohareb, R. M.; Neder, R. B.; Schwabenlander, F.; Telser, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4521-37. c) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615-7. d) Morie, T.; Kato, S. *Heterocycles* **1998**, *48*, 427. e) Albertini, E.; Barco, A.; Benetti, S.; DeRisi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1997**, *53*, 17177. f) Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693. g) Tuch, A.; Saniere, M.; LeMerrier, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, 7, 2901. h) Müller, A.; Takyar, D. K.; Witt, S.; König, W. A. *Liebigs Ann. Chem.* **1993**, 651.

10 a) Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385-6. b) Nadin, A.; Derrer, S.; McGeary, R. P.; Goodman, J. M.; Raithby, P. R.; Holmes, A. B.; O'Hanlon, P. J.; Pearson, N. D. *J. Am. Chem. Soc.* **1995**, *117*, 9768-9. c) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393-6. d) Colombo, L.; Di Giacomo, M.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.* **1994**, *35*, 4031-4.

11 a) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368-70. b) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831-43.

12 Gawley, R. E.; Rein, K. Alkylations of Nitrogen-stabilized Carbanions. In *Carbon-carbon σ Bond formation*; Trost, B. M., Ed.; Comprehensive Organic Synthesis, Vol 3; Pergamon Press: Oxford, 1991; 65-83.

13 a) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270-6. b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

14 Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109-17. b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231-9.

15 a) White, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6605-7. b) Kaga, H.; Miura, M.; Orito, K. *Synthesis* **1989**, 864-6.

16 Chris Rithner is gratefully recognized for obtaining the nOe spectra of compounds **2.48** and **2.49**.

17 Susie Miller is gratefully recognized for solving the X-ray crystal structures of compounds **2.48** and **2.64**.

18 Farmer, E. H.; Kracouski, J. *J. Chem. Soc.* **1927**, 680-685.

19 Claus, R. E., Schreiber, S. L. *Org. Synth.* Vol *64*, 150.

20 The diagnostic 300 MHz ^{1}H NMR signals for phenylglycinol in $CDCl_3$, even as a mixture with methyl 6-oxohexanoate, are seen at 3.55 (dd, 1H), 3.73 (dd, 1H), and 4.33 (dd, 1H). These peaks were observed at 4.09 (apt t, 1H), 4.61 (dd, 1H), and 5.16 (apt t, 1H) in the crude product, and are consistent with those observed in the 5,7-bicyclic structures.

21 a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974-8. b) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. No. VII, 530. c) Meyers, A. I.; McKennon, M. J. *J. Org. Chem.* **1993**, *58*, 3568-71. d) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.

22 a) Weast, R. C. *CRC Handbook of Chemistry and Physics, 1st Student ed.*; CRC Press, Inc.; Boca Raton, Florida, 1988, pp D1-33, E44-46. b) Aldrich Catalog and Handbook of Fine Chemicals, 1996/1997.

23 The relative polarity of the solvents examined was heptane < benzene, toluene, xylenes < EtOAc < lutidine < *n*-BuOH < MeOH < MeCN, based on comparison of their dielectric constants.[22,24]

24 Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 3rd ed. Part A: Structure and Mechanisms*; Plenum Press: New York, 1990, pp 141, 158, 163-167, 233.

25 a) Yamada, S.; Wagatsuma, M.; Takeuchi, Y.; Terashima, S. *Chem. Pharm. Bull.* **1971**, *19*, 2380-8. b) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. c) Nadin, A. I., et. al. *Materials Science and Engineering C* **1996**, *4*, 59.

26 Beugelmans, R.; Ginsburg, H. *Heterocycles* **1985**, *23*, 1197.

27 a) Bromination: Haworth, R. D.; Perkin, W. H. Jr. *J. Chem. Soc.* **1925**, *127*, 1448. b) Iodination: Cromartie, R. I. T.; Harley-Mason, J.; Wannigama, D. G. P. *J. Chem. Soc.* **1958**, 1982.

28 Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507-15.

29 Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317-4352.

30 Zouaoui, M.; Mouaddib, A.; Jamart, G. B.; Ianelli, S.; Nardelli, M.; Caubere, P. *J. Org. Chem.* **1991**, *56*, 4078-81.

31 Meyers, A. I.; Hanreich, R.; Wanner, K. Th. *J. Am. Chem. Soc.* **1985**, *107*, 7776-8.

32 Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 858.

33 The $Pd(PPh_3)_4$ mediated elaboration of potassium enolates using iodobenzene (ref a,b) or a vinyliodide (ref c) has been reported: a) Ciufolini, M. C.; Qi, H.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149-51. b) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506-8. c) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454-5.

34 Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011-4.

35 a) Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541-4.

36 a) The 300 MHz ^{1}H NMR resonances for the angular methyl protons are found at 1.19 ppm in the major epimer and at 1.09 ppm for the minor epimer. b) The 300

MHz ^{1}H NMR resonances for the angular methyl protons in α,α-disubstituted lactams **2.78**, **2.79a**, and **2.79b** are all upfield (1.09 ppm, 1.13 ppm, 1.14 ppm, respectively) of those for α-monosubstituted lactams **2.71** (1.49 ppm) and **2.72** (1.51 ppm).

37 Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.

38 a) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765-8. b) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press, Inc.: San Diego, CA, 1992. c) Dowd, P.; Choi, S.-C. *Tetrahedron* **1991**, *47*, 4847-60.

39 Yet, L. *Tetrahedron* **1999**, *55*, 9349-403.

40 Lefker, B. A. The Synthesis of Asymmetric Quaternary Carbon Centers via Bicyclic Lactams. Ph.D. Dissertation, Colorado State University, Fort Collins, CO, Fall 1988. pp 98-108.

41 Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633.

42 a) Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 4124-7. b) Bordwell, F. G.; Jarvis, B. B. *J. Org. Chem.* **1963**, *33*, 1182-5.

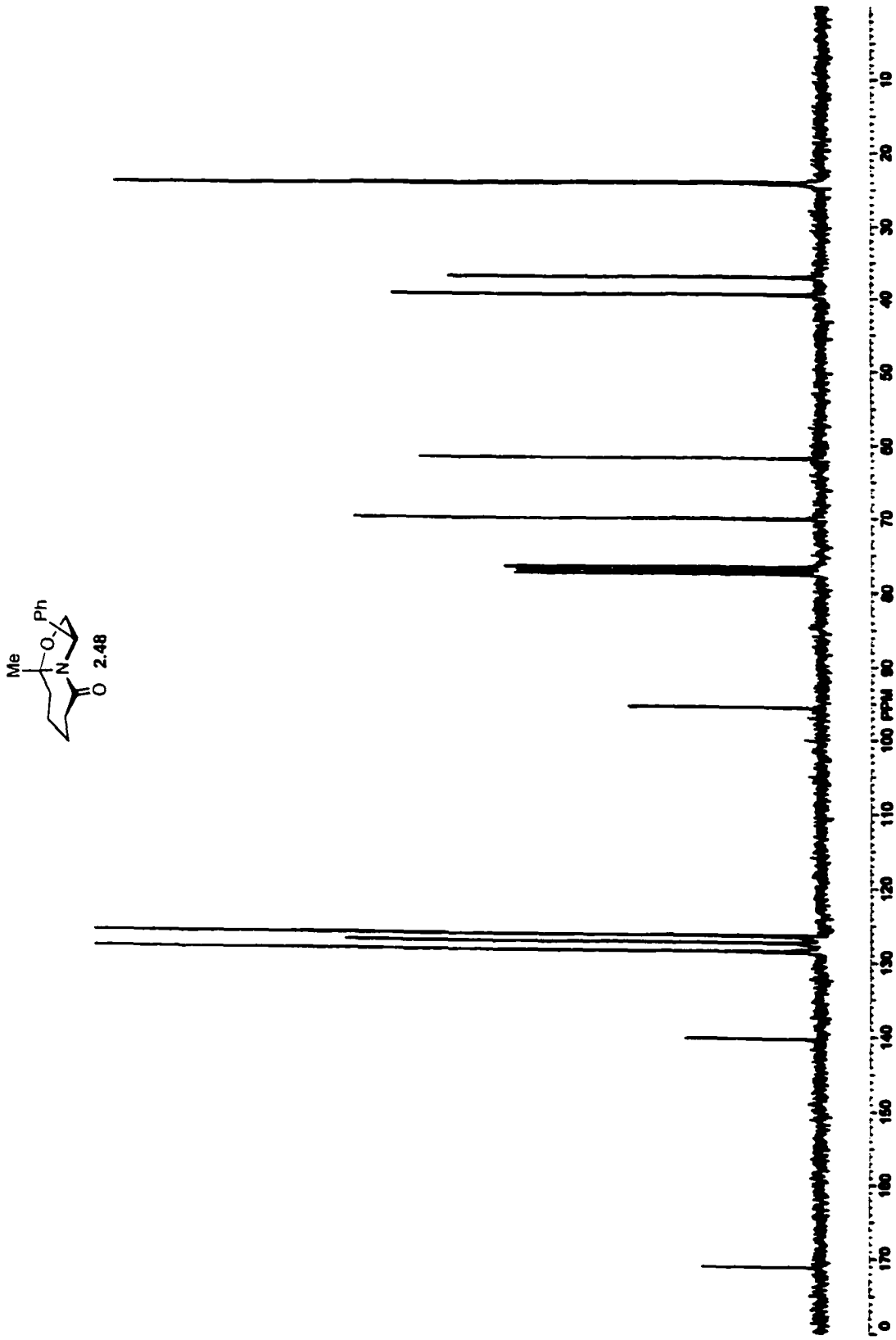
43 The chemistry for the ring closing metathesis route to lactam **2.48** was brought to fruition by Michael J. Weiser, working under the supervision of Michael D. Groaning.

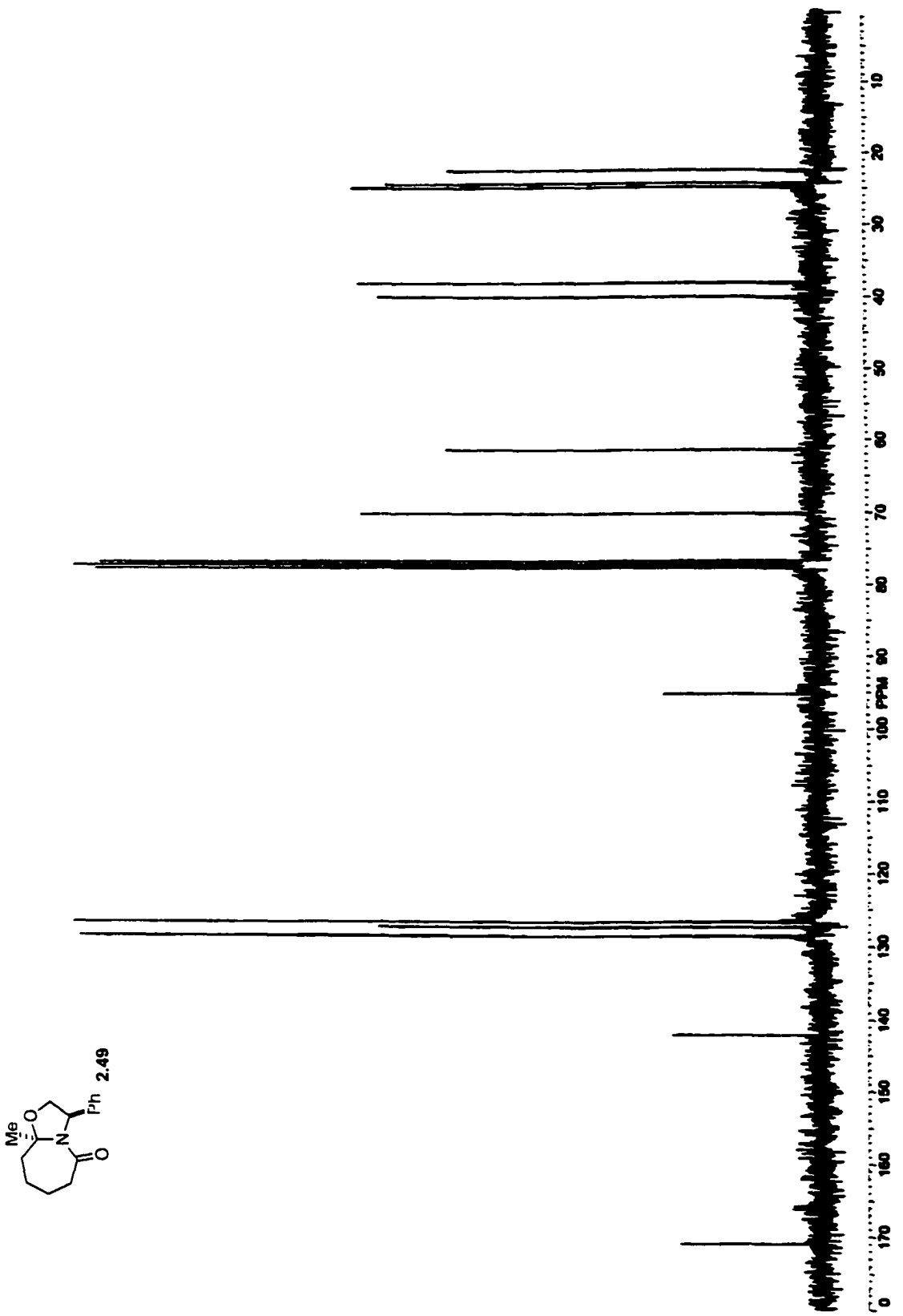
44 Barrett, A. G.; et al. *J. Org. Chem.* **1998**, *63*, 7893-907.

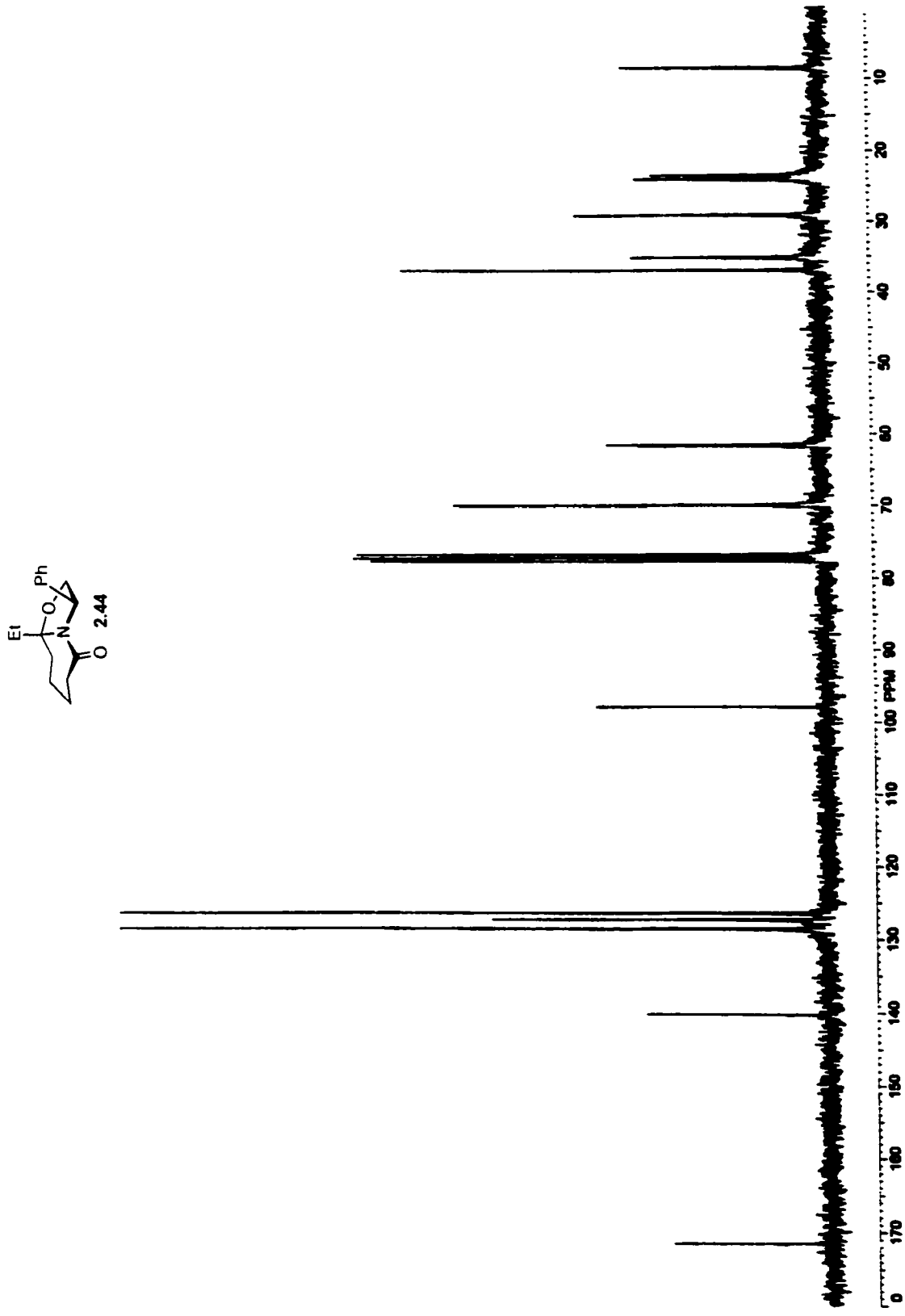
45 Agnete la Cour is gratefully recognized for solving the X-ray crystal structure of compound **(–)-2.96**, for which the absolute structure parameter is 0.00±0.19. After refinement of the structure as the *S*-enantiomer, the flack parameter was 1.20±0.18. Designation of *C*-5 as nitrogen and *N* as *C*-5 resulted in an unreliable temperature factor and a rise of the conventional R-factor from 0.0764 to 0.0839. Upon refinement of the crystal structure as a racemic twin, the data converged to 100% of the *R*-enantiomer, with a confidence level of 95%.

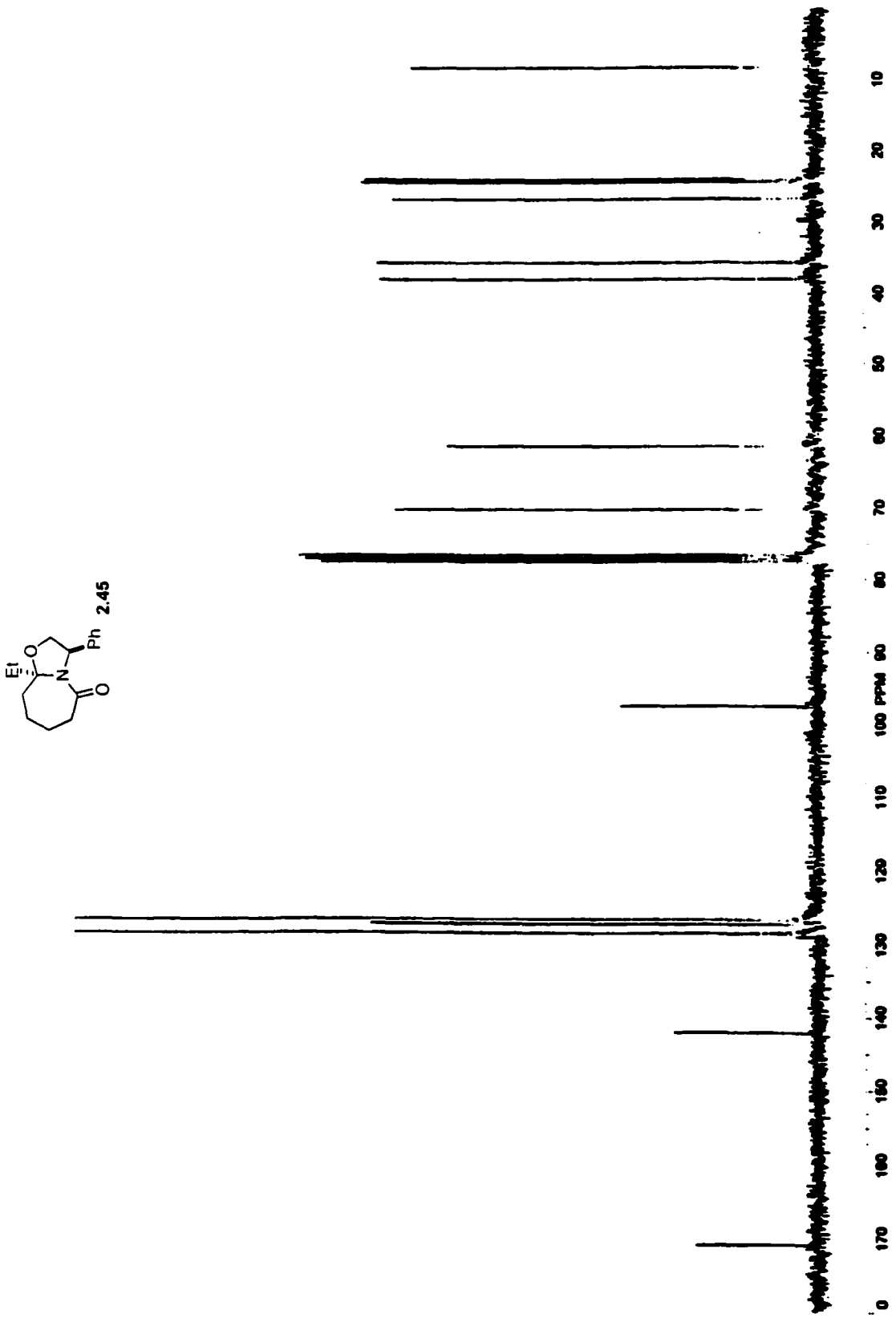
46 Legrand, M.; Rougier, M. J. Application of the Optical Activity to Stereochemical Determinations. In *Determination of Configurations by Dipole Moments, CD or ORD*; Kagan, H. B. Ed.; Stereochemistry: Fundamentals and Methods, Vol. 2; Georg Thieme Publishers: Stuttgart, 1977; 41-47.

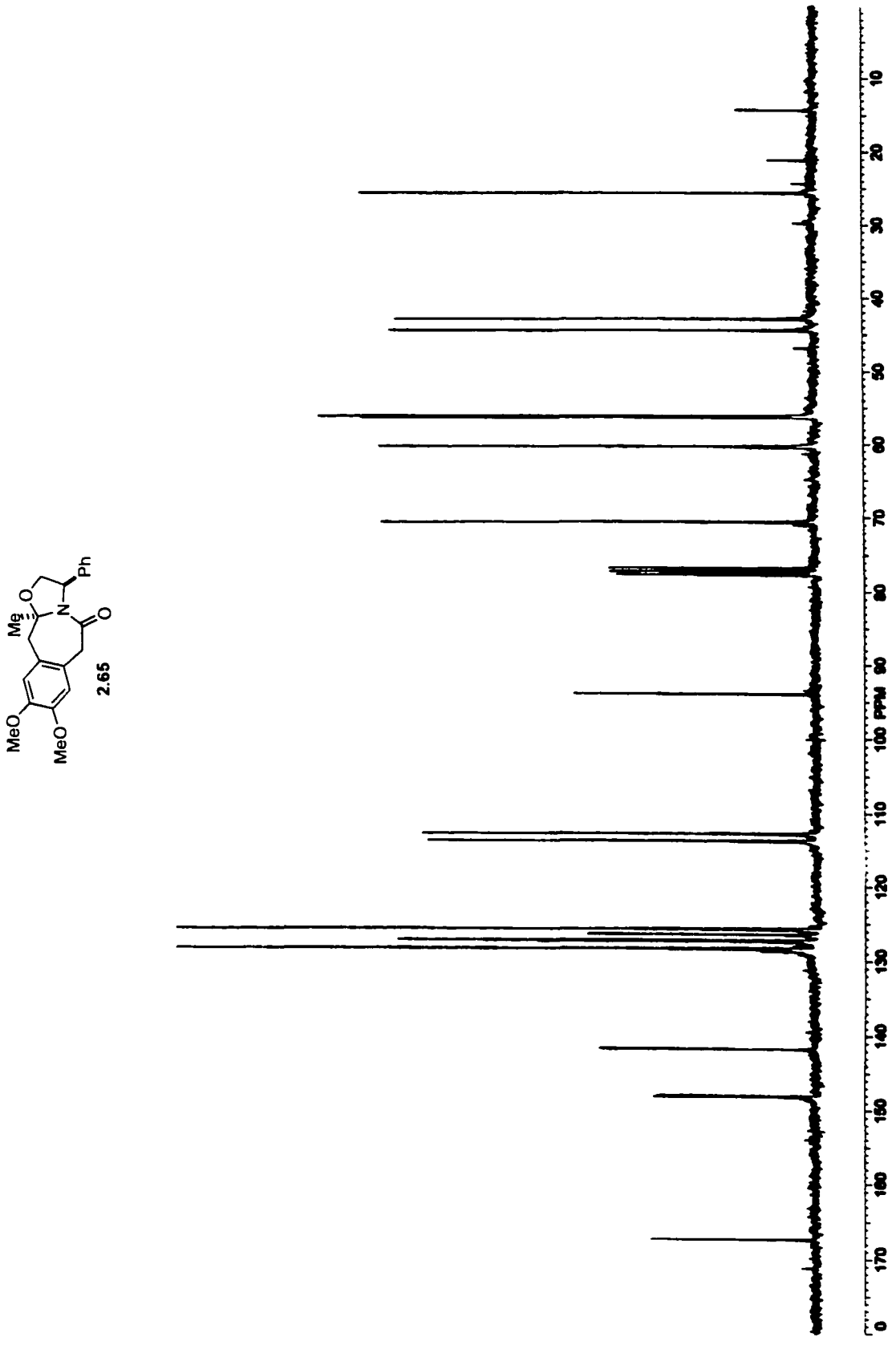
V. NMR Spectra and Single Crystal X-ray Data

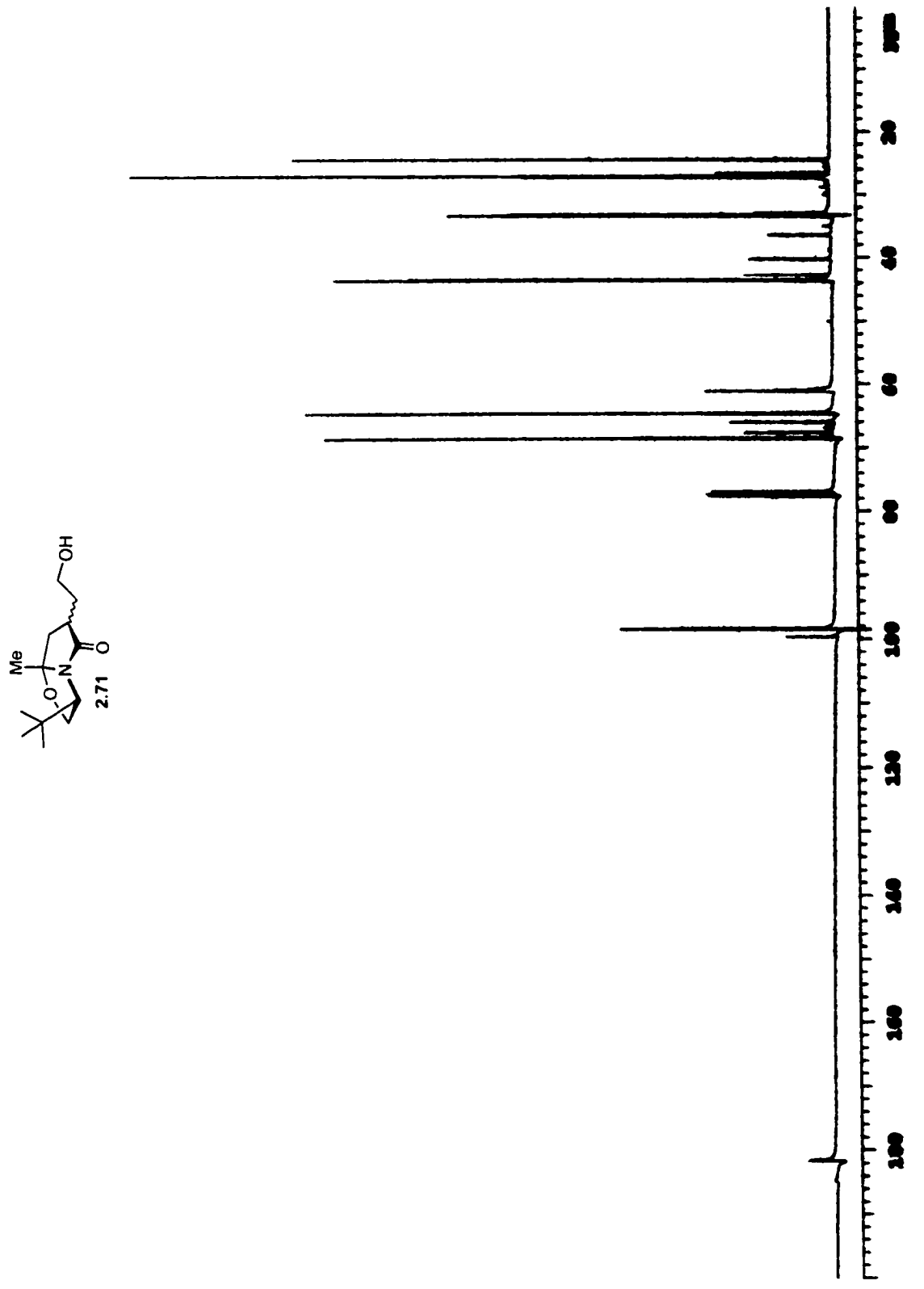


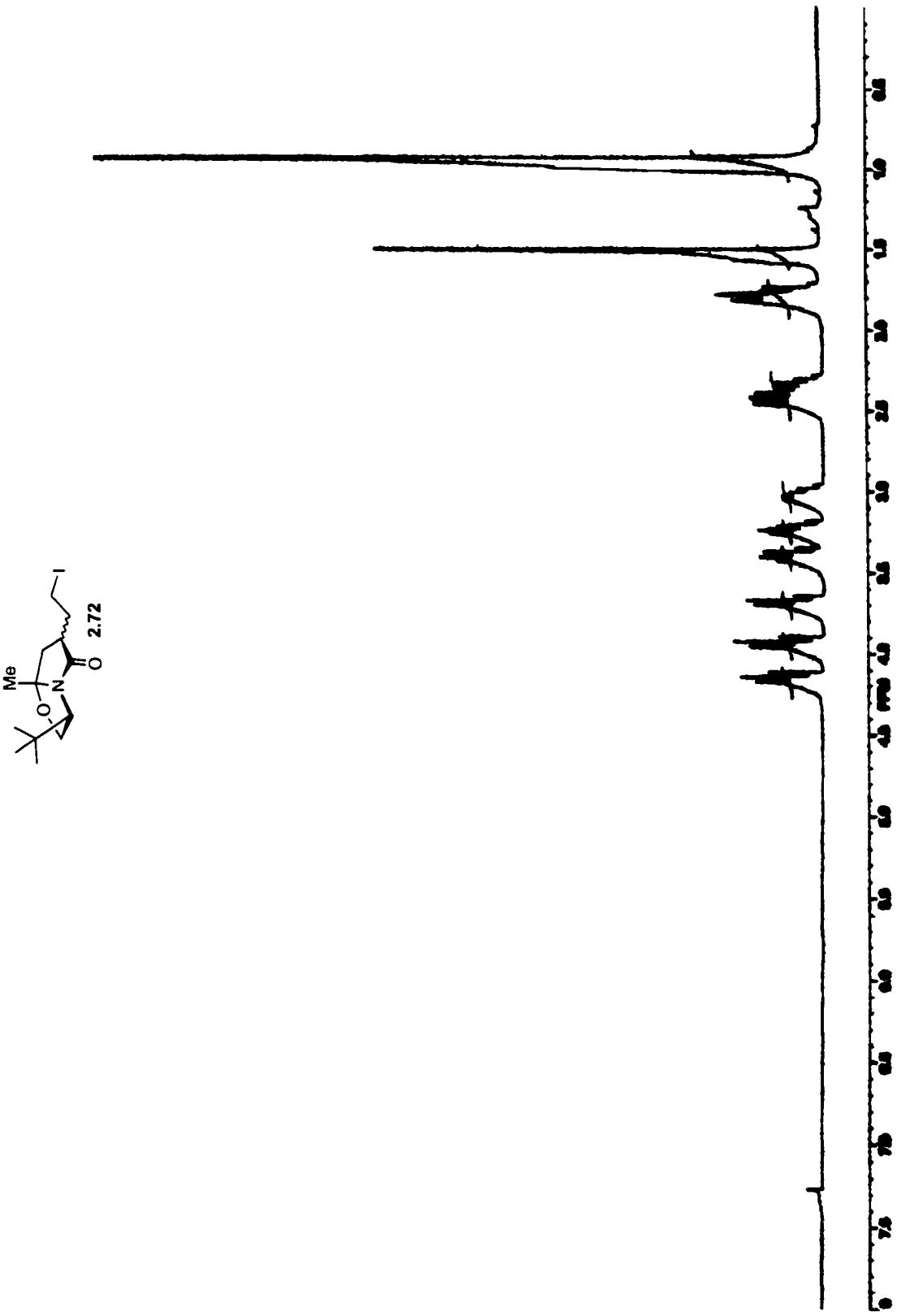


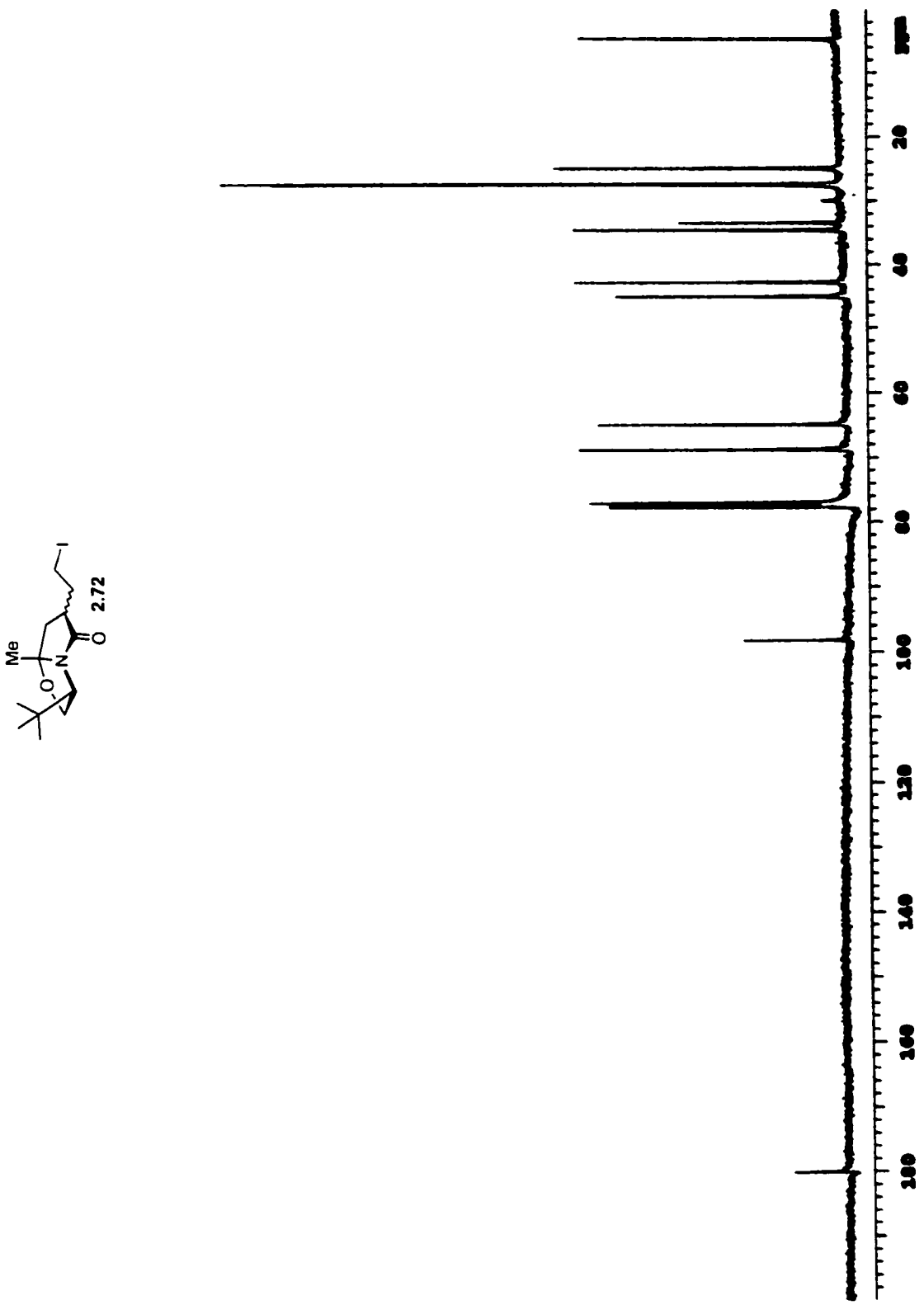


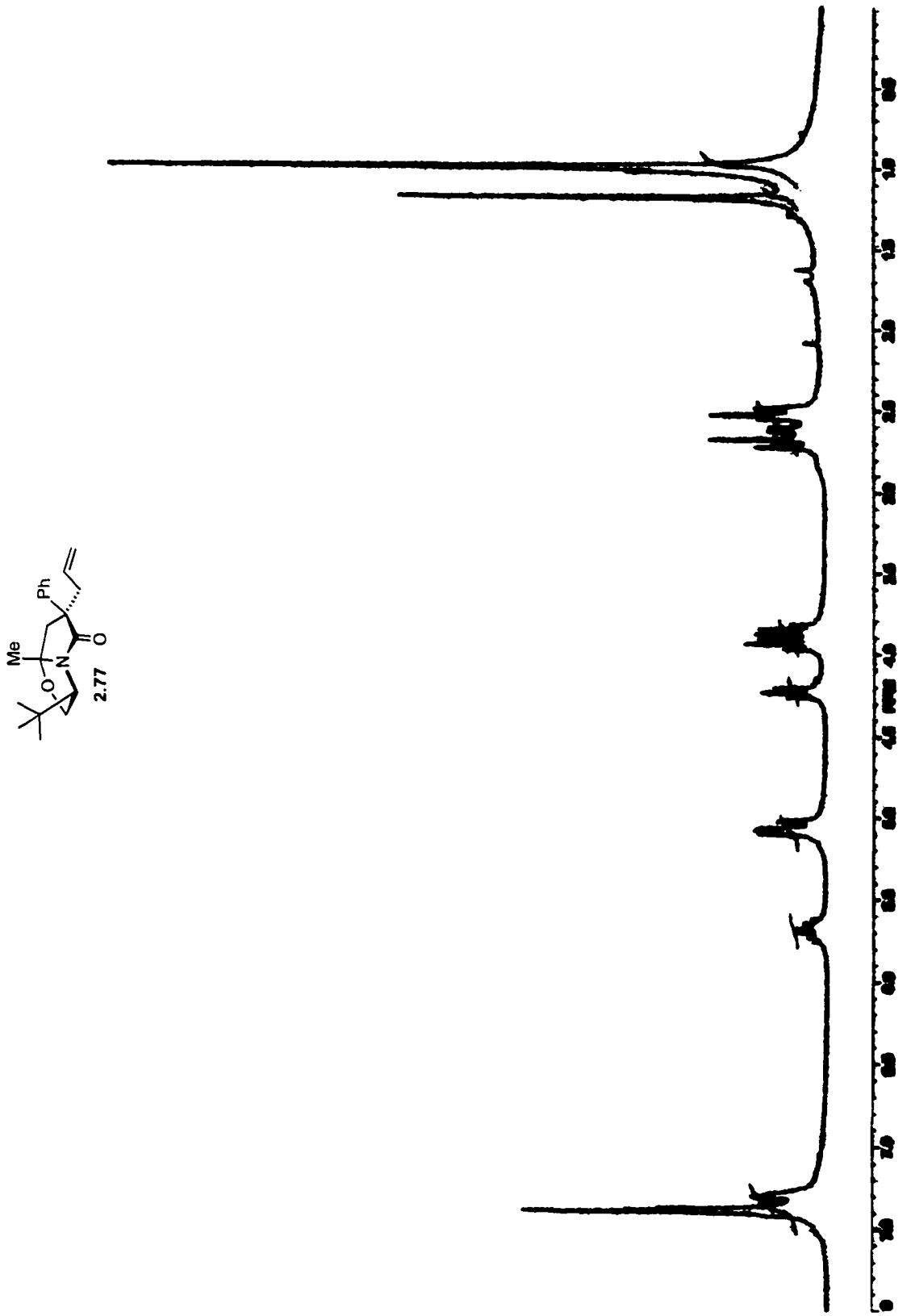


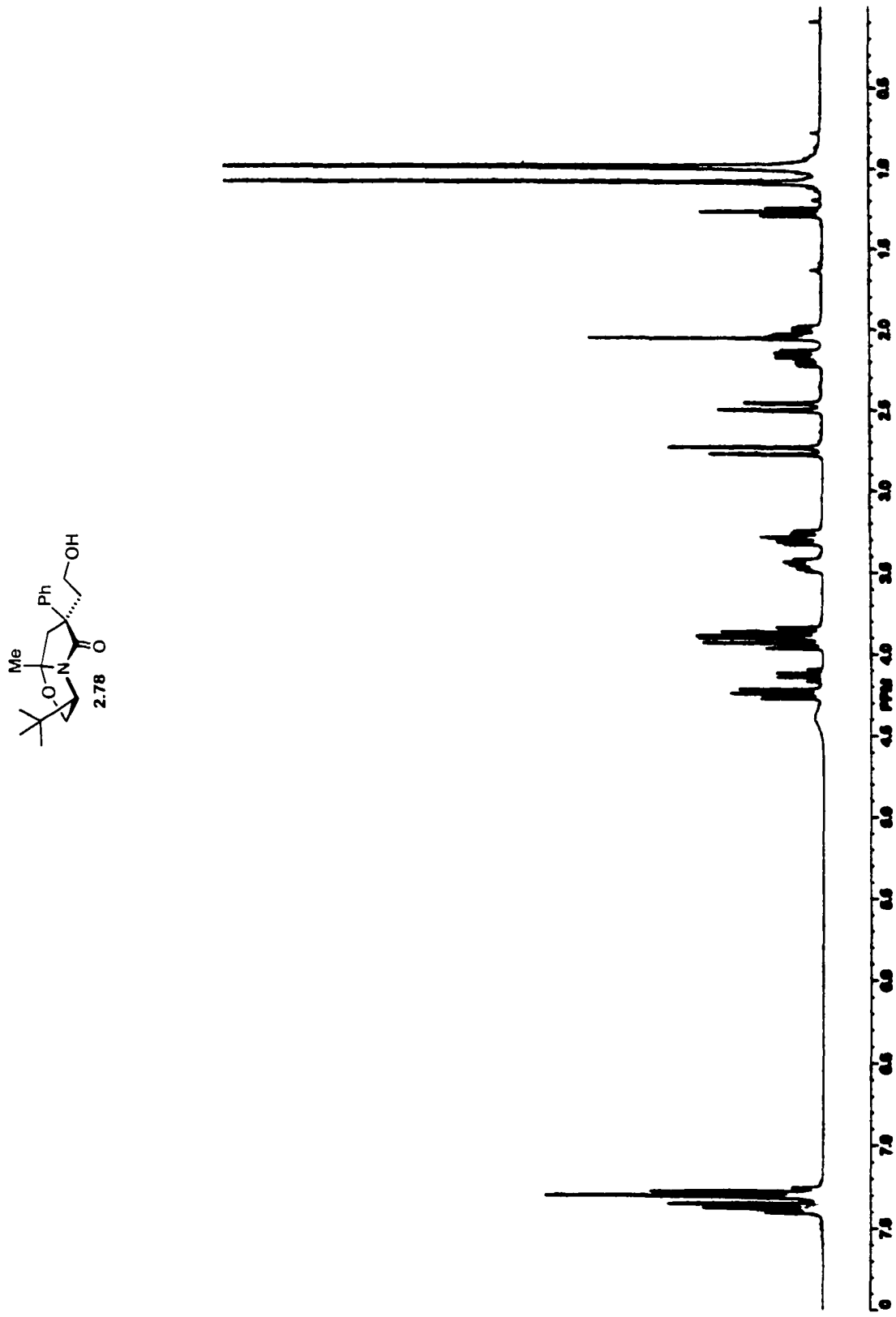


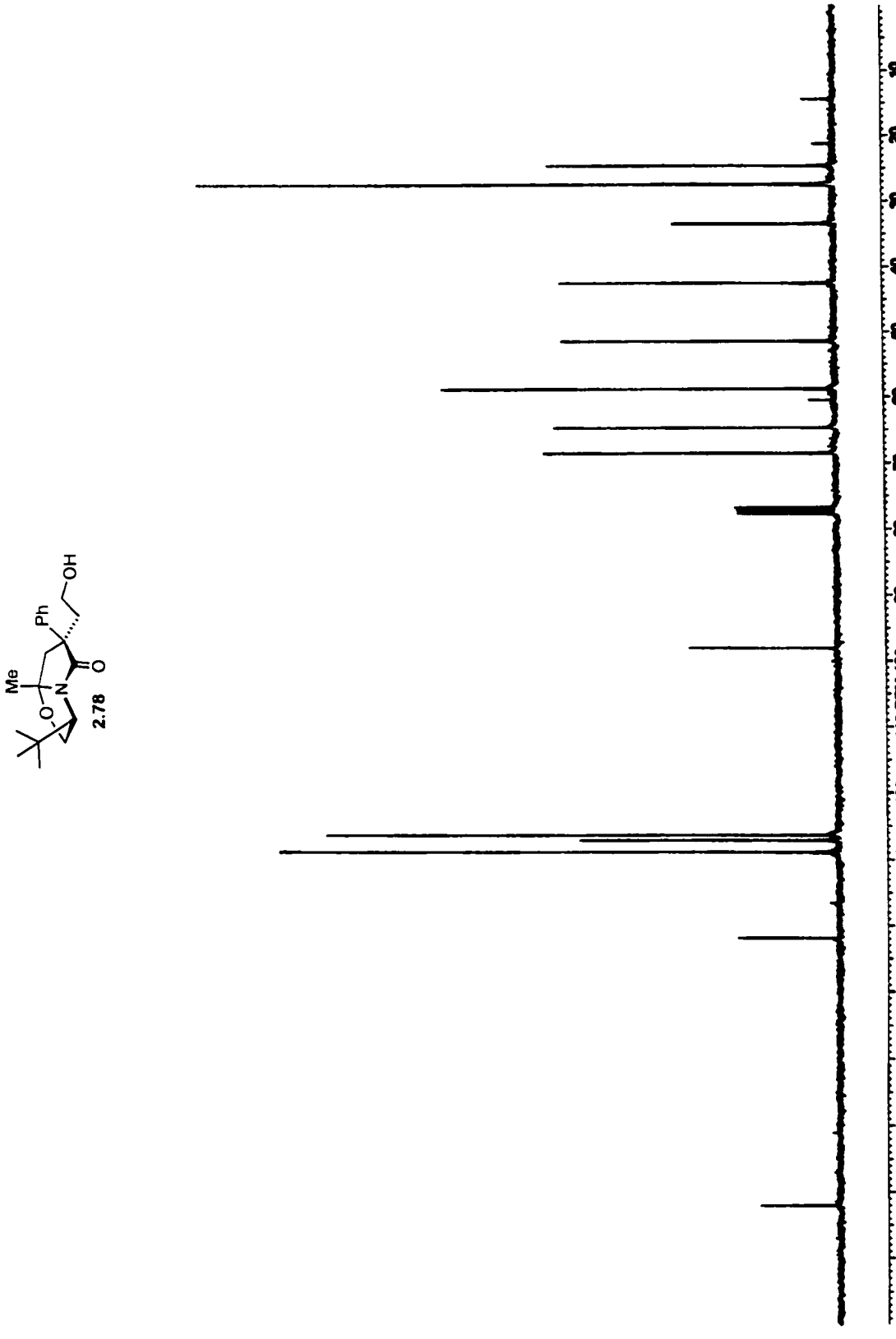


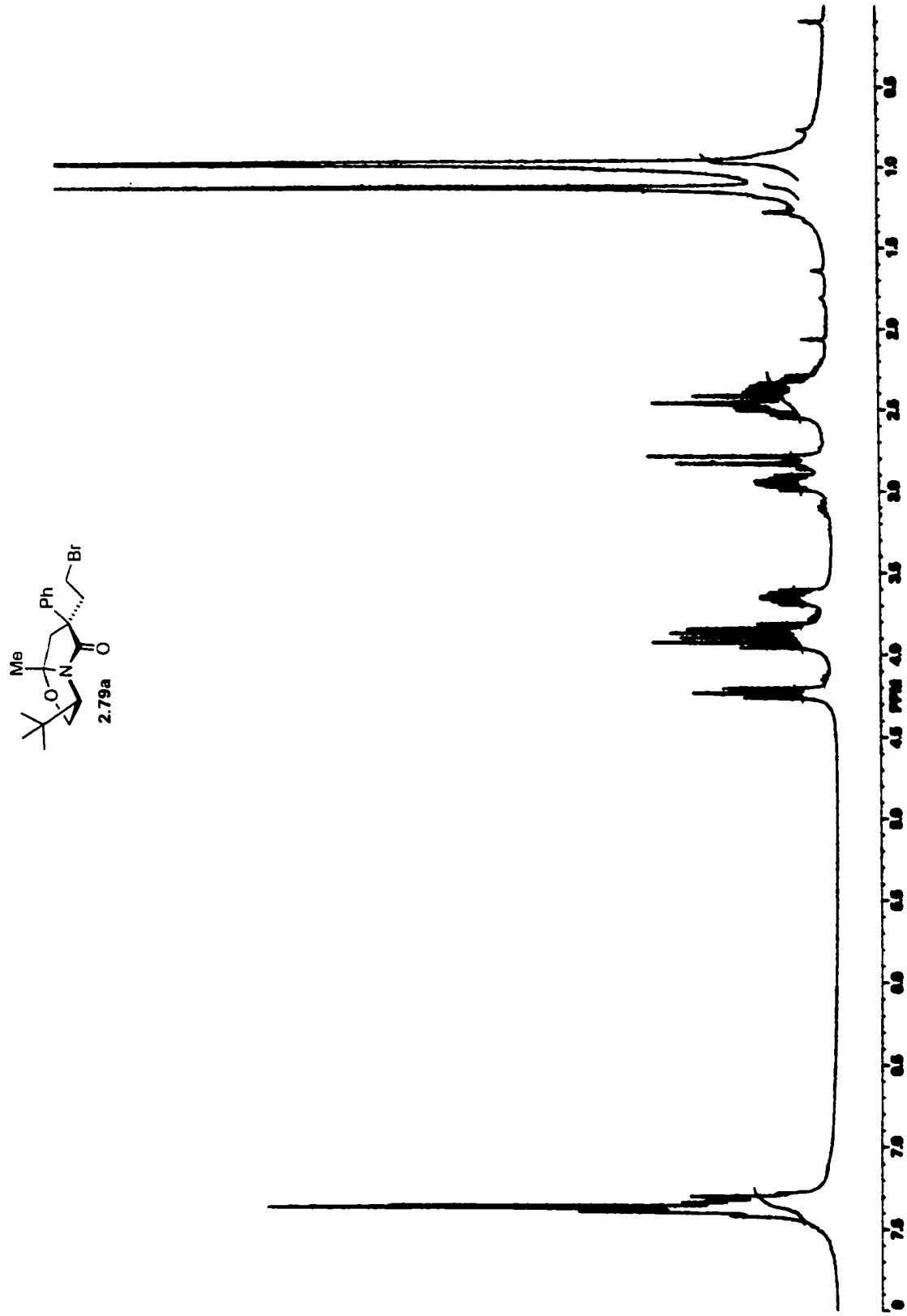


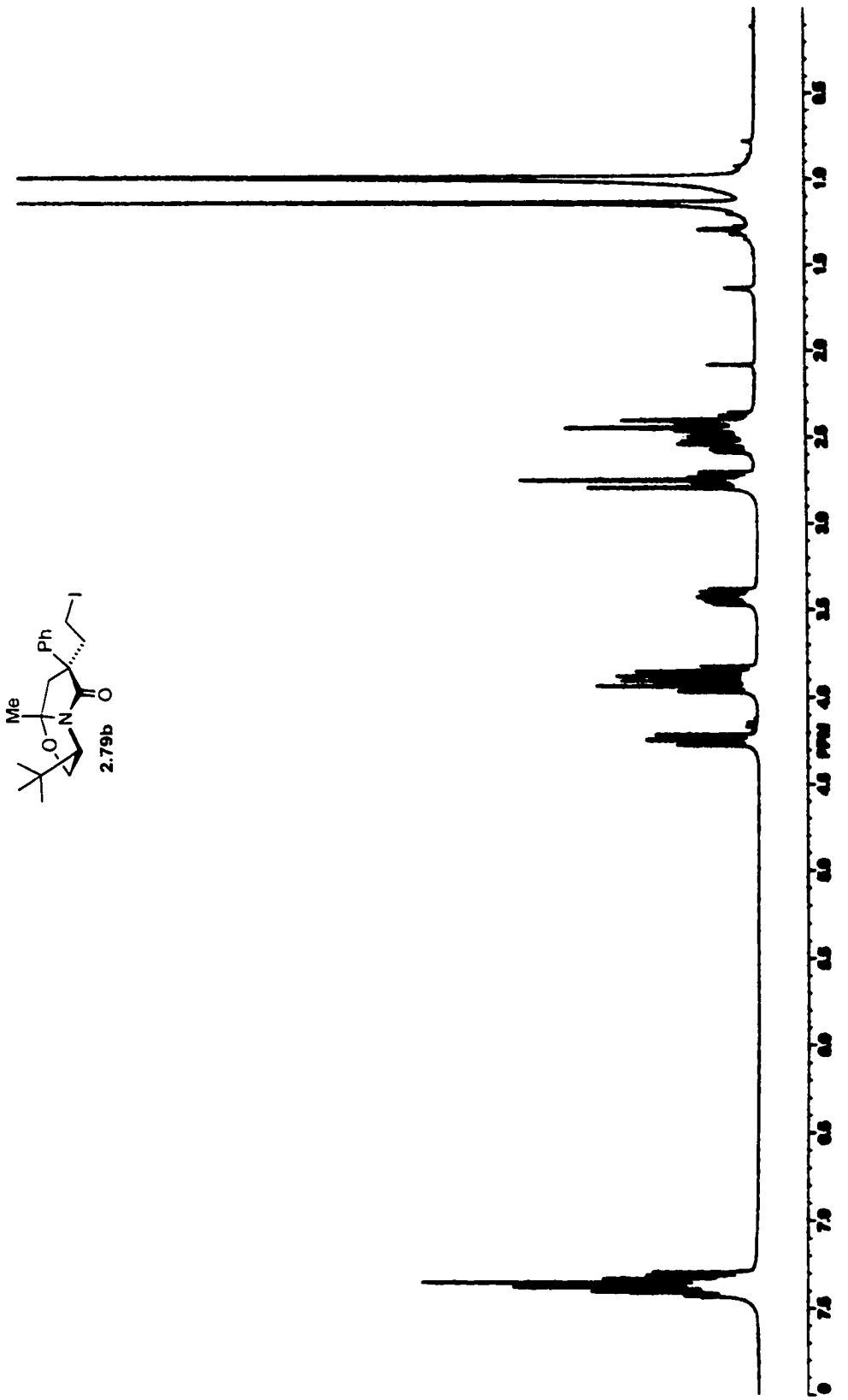


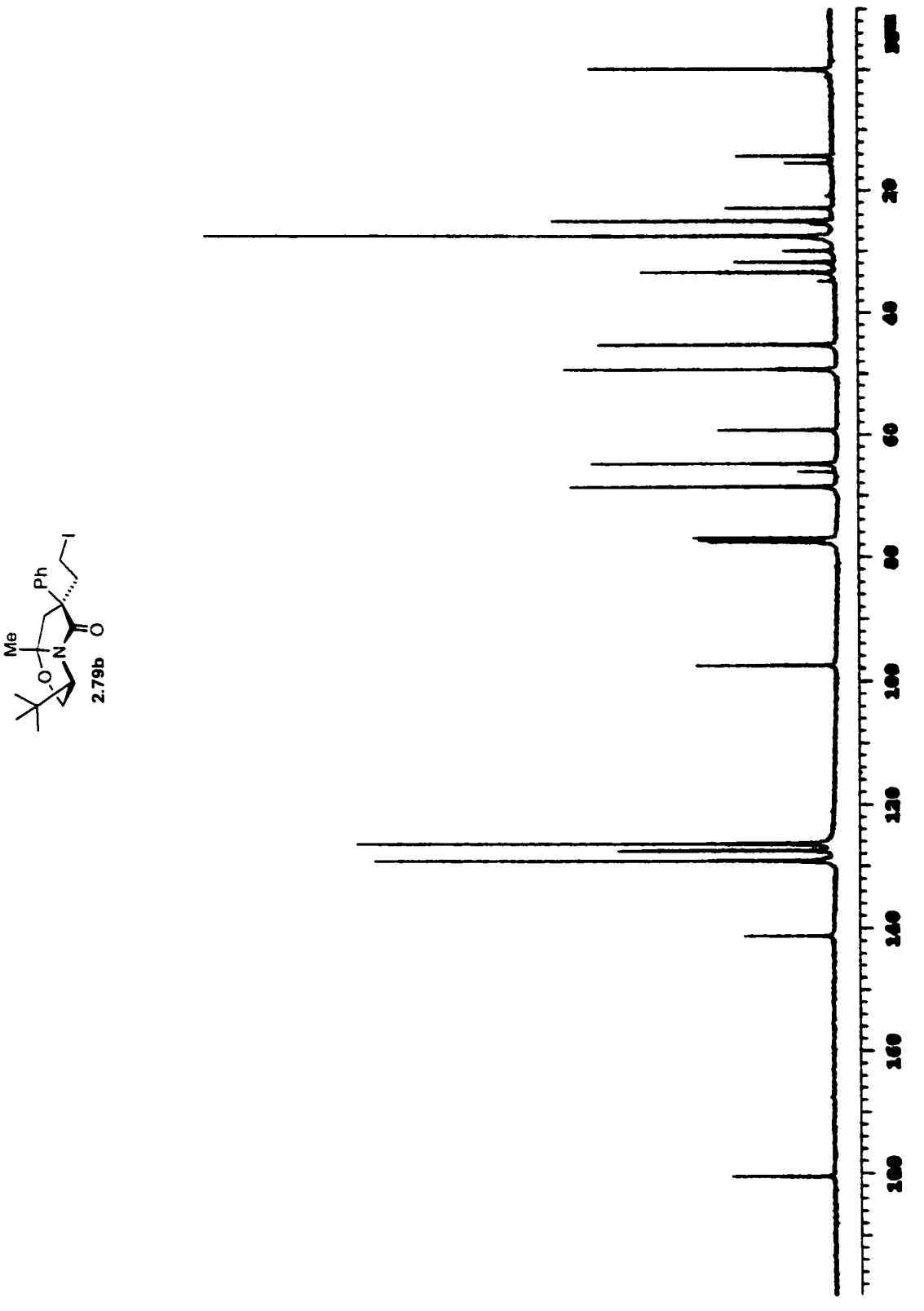


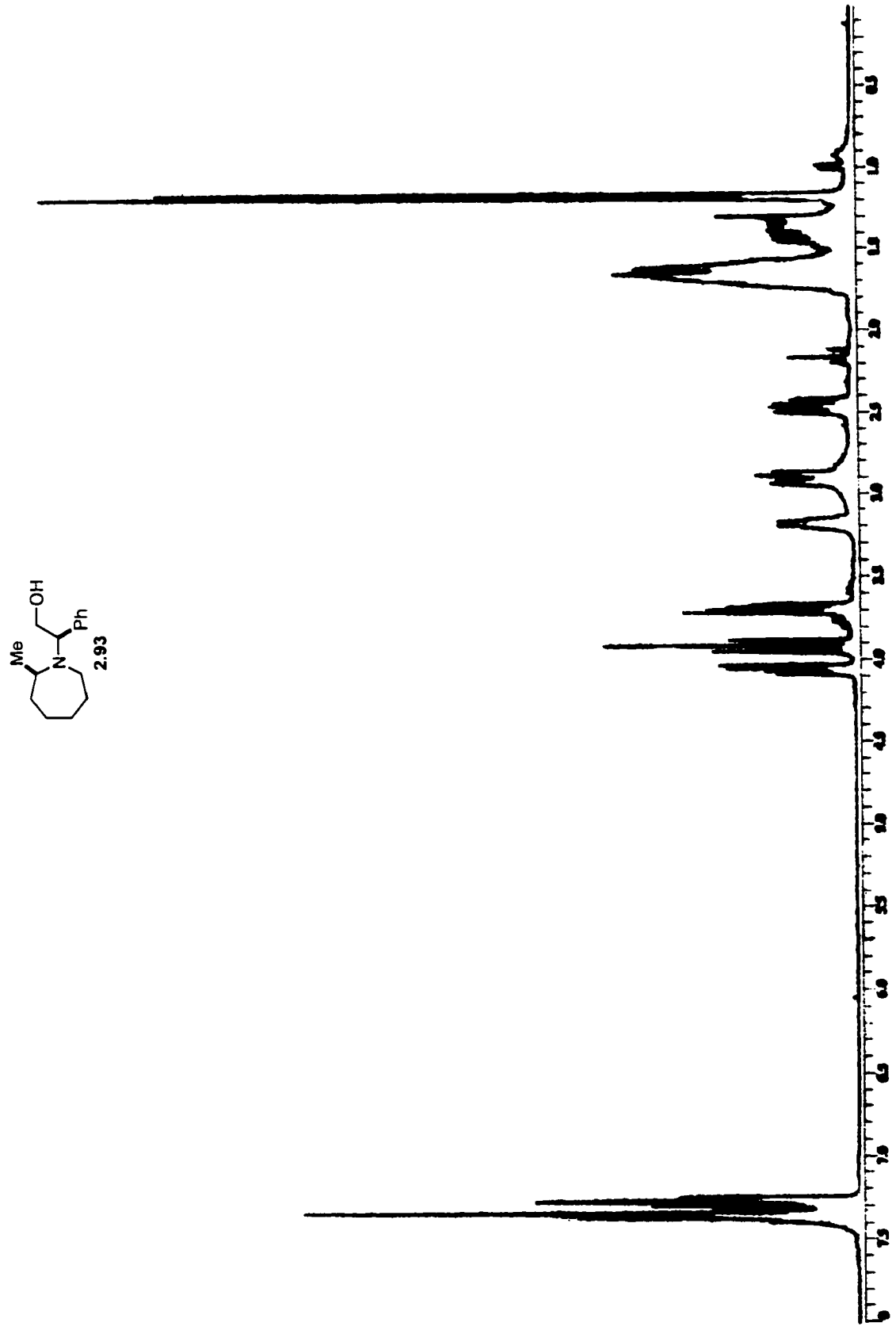


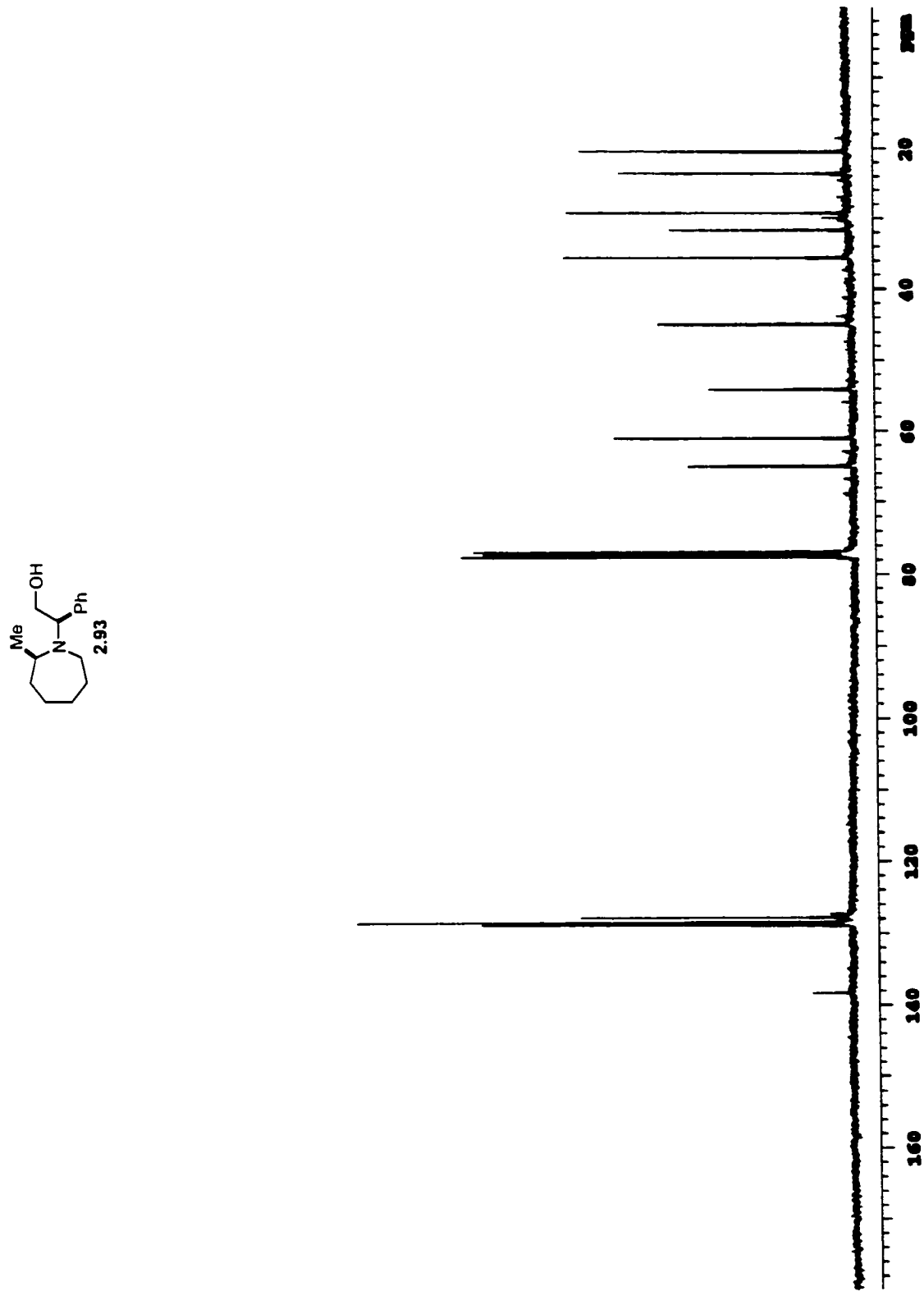


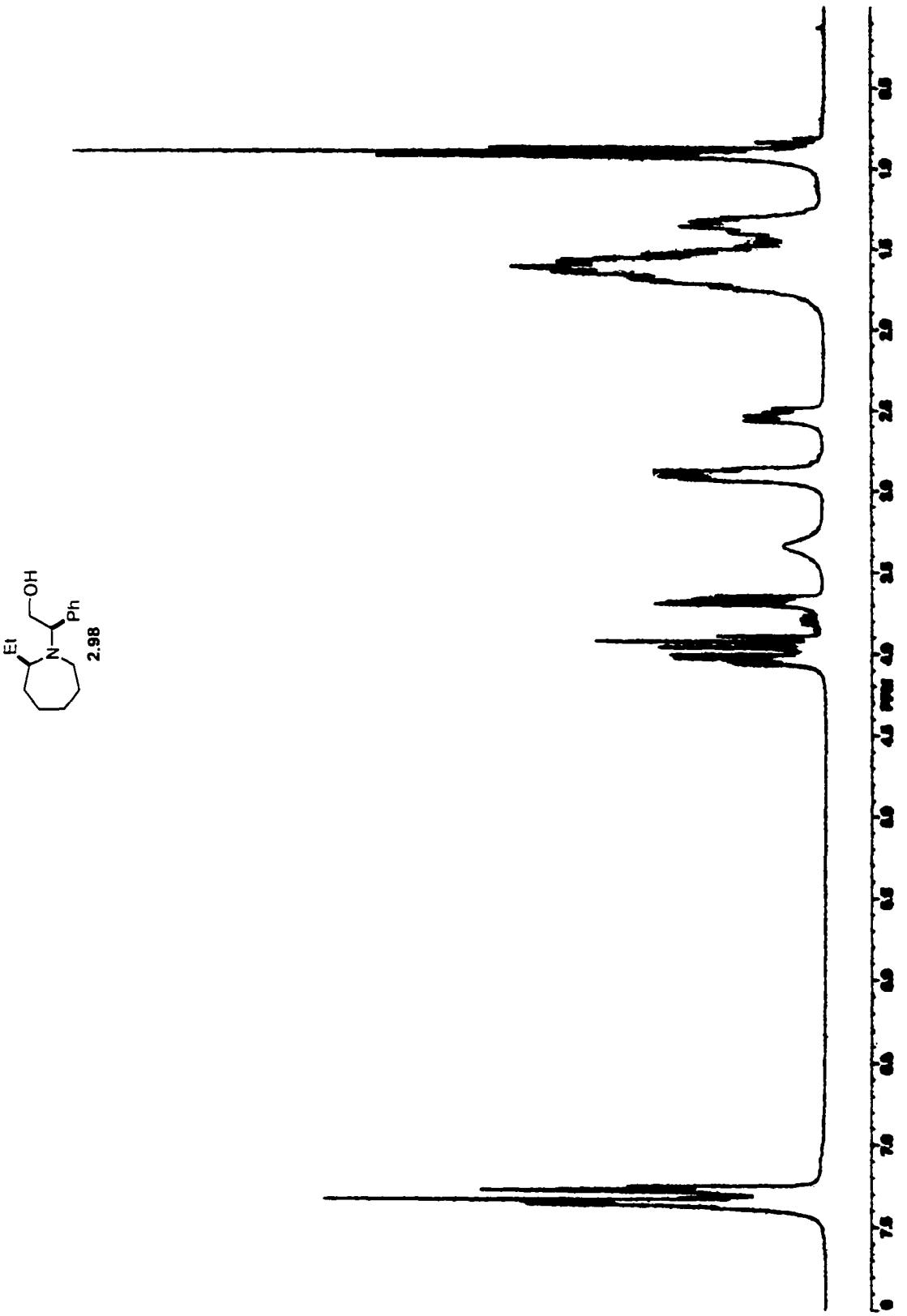


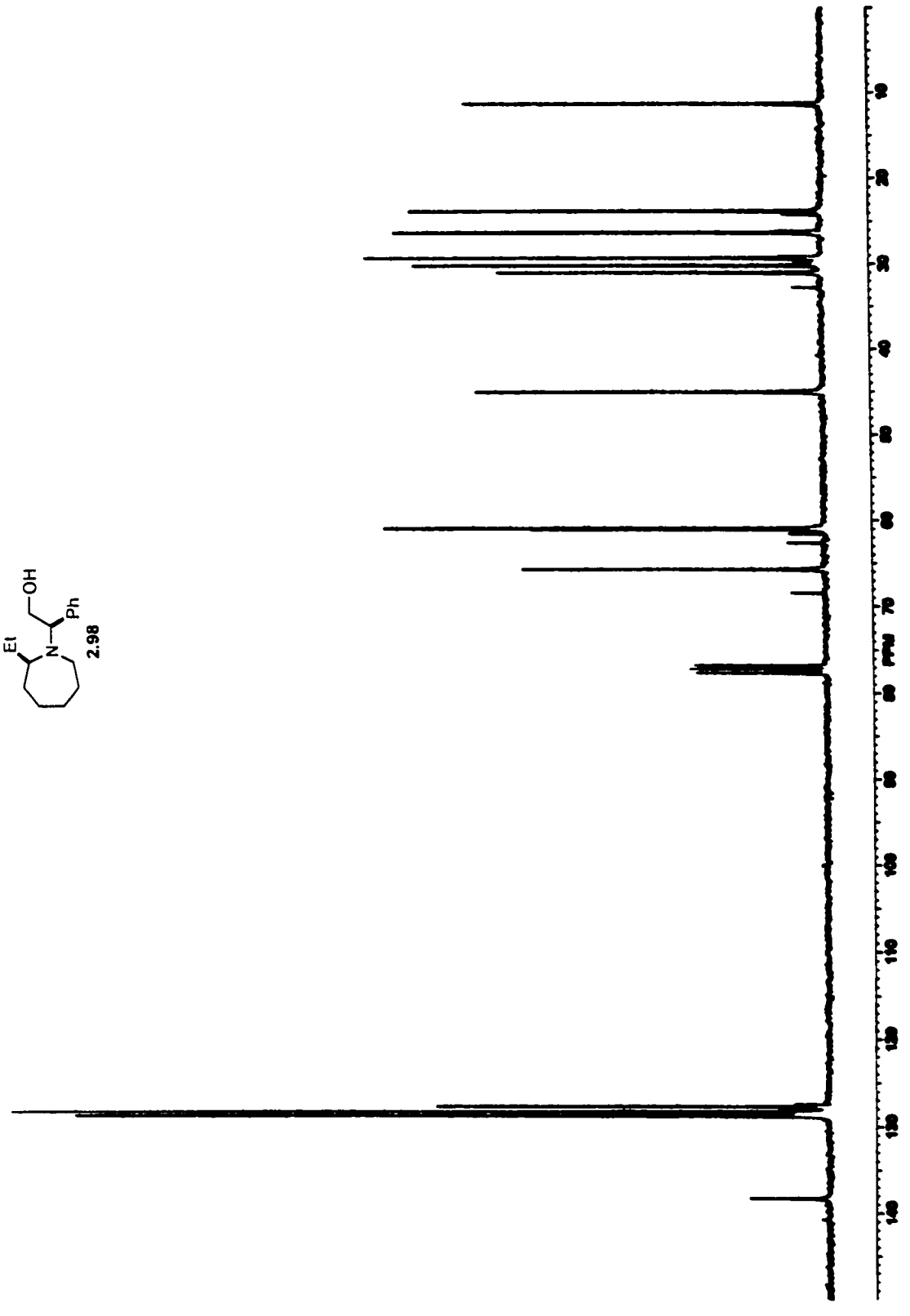


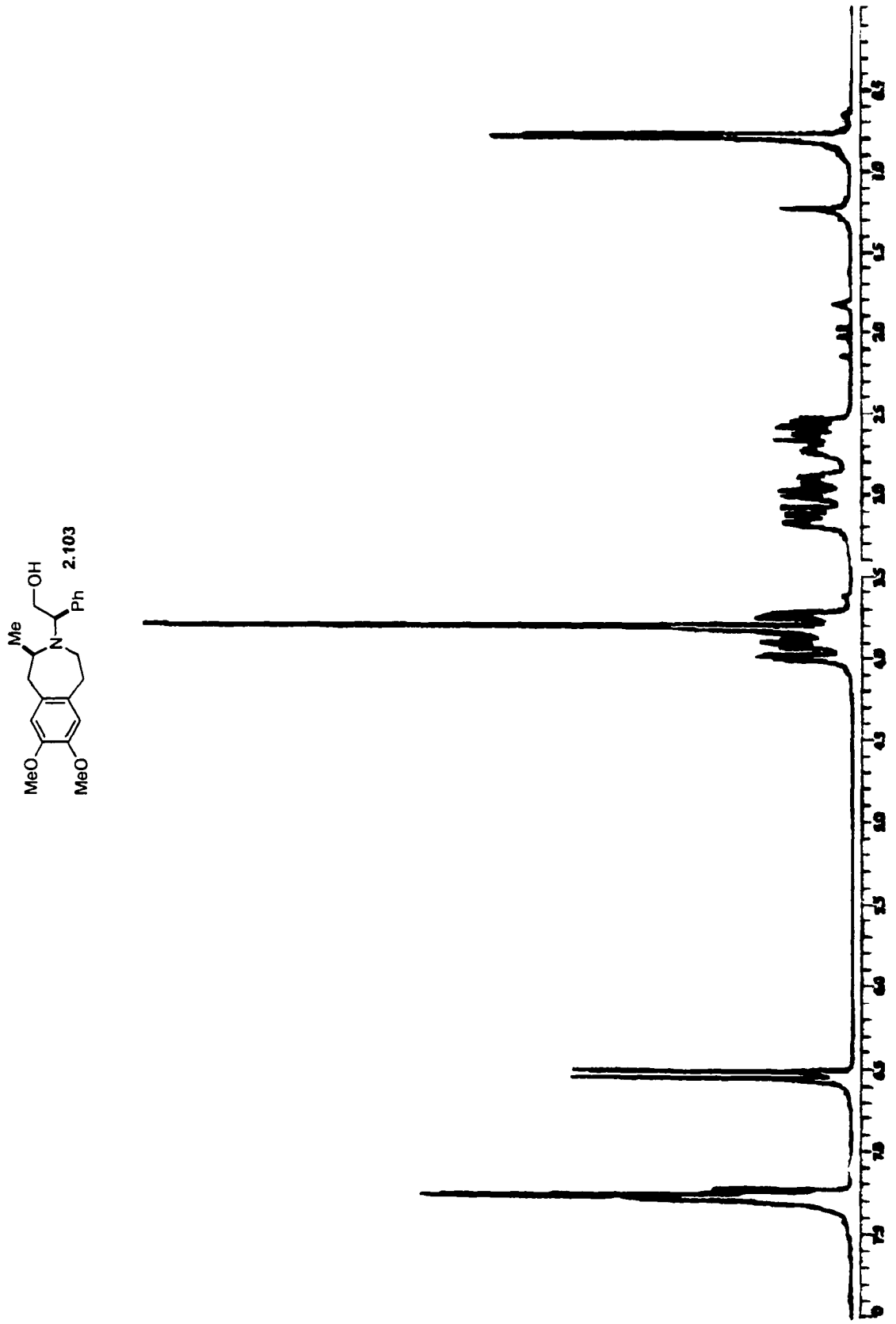


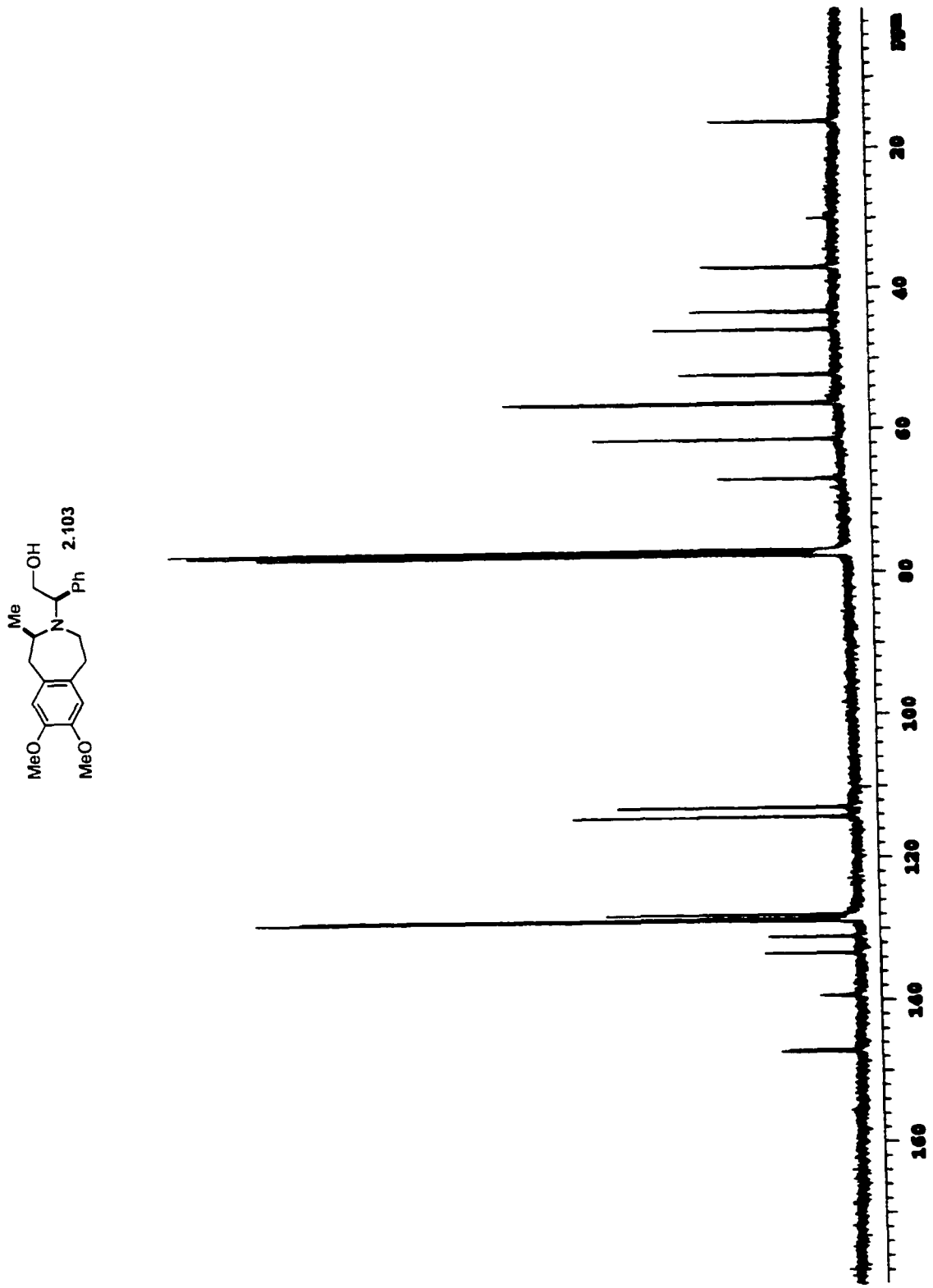


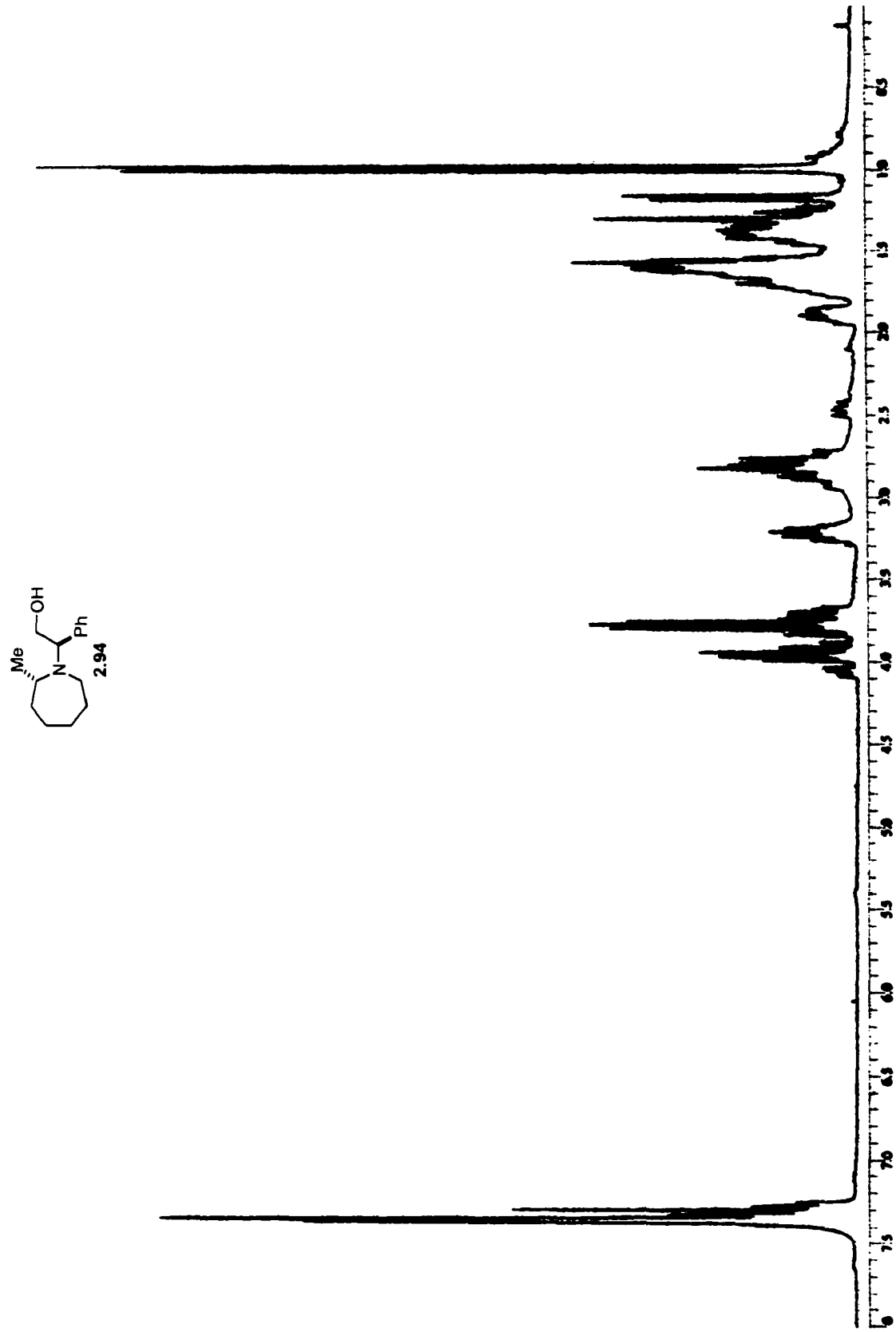


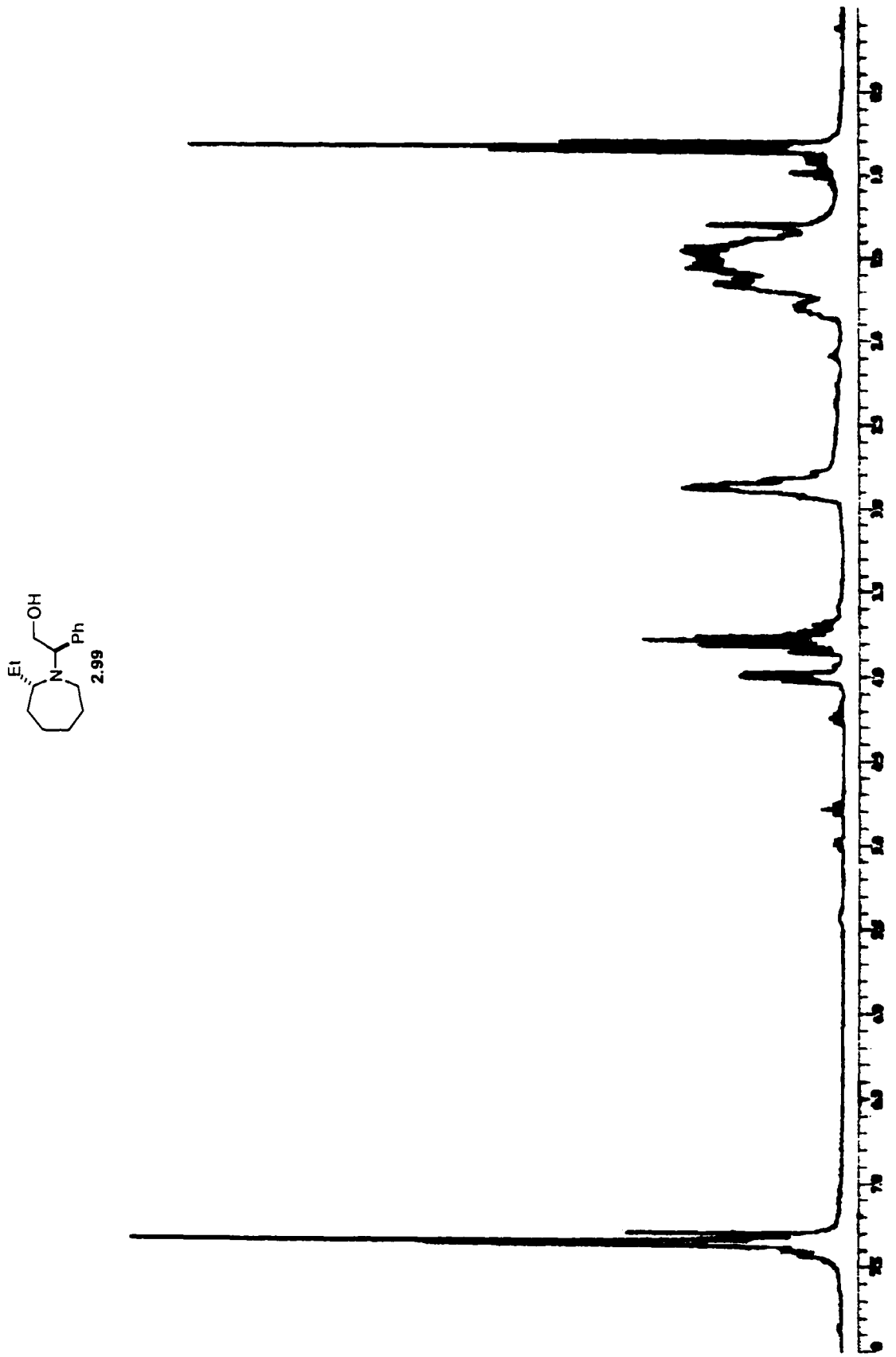


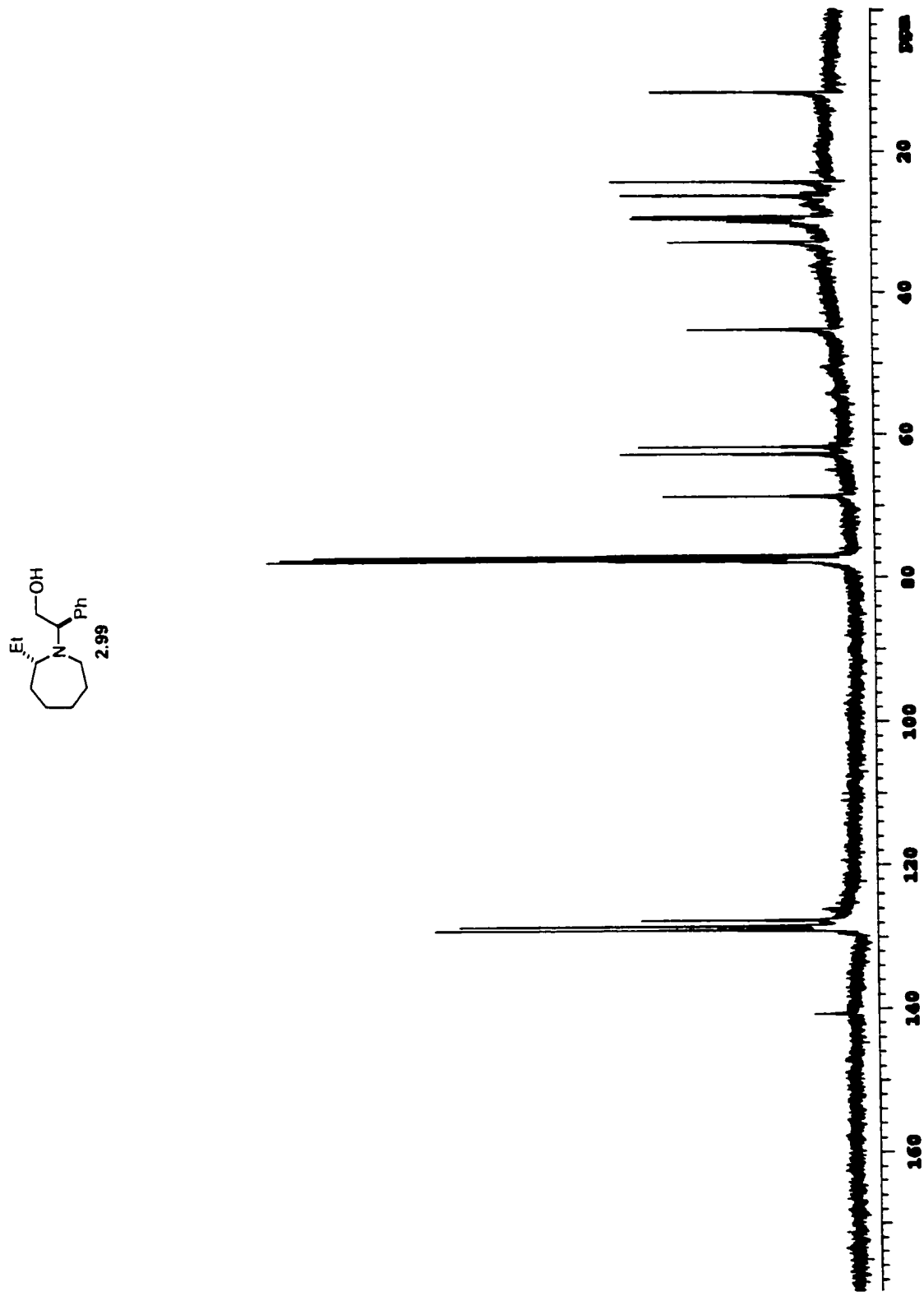


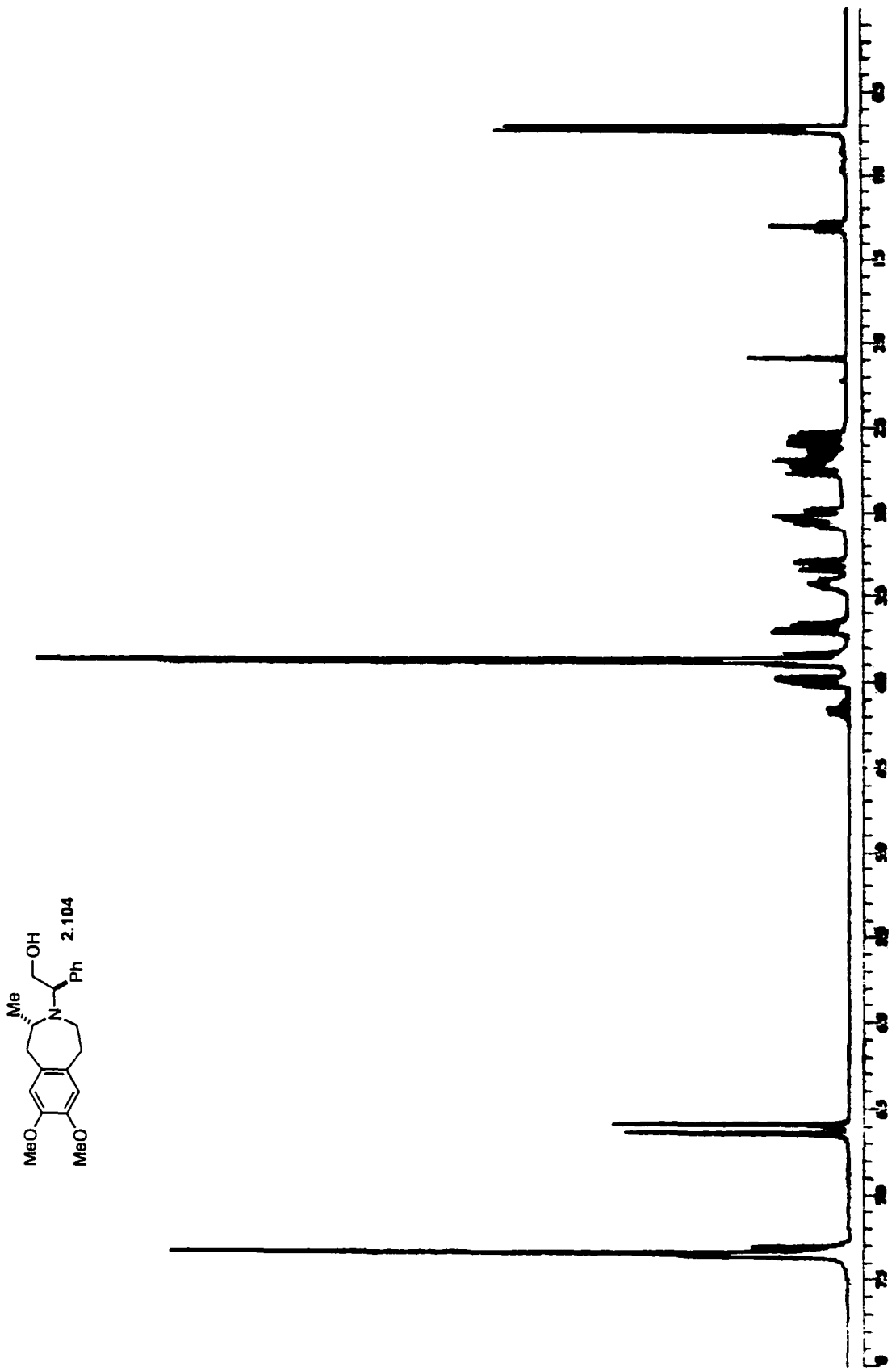


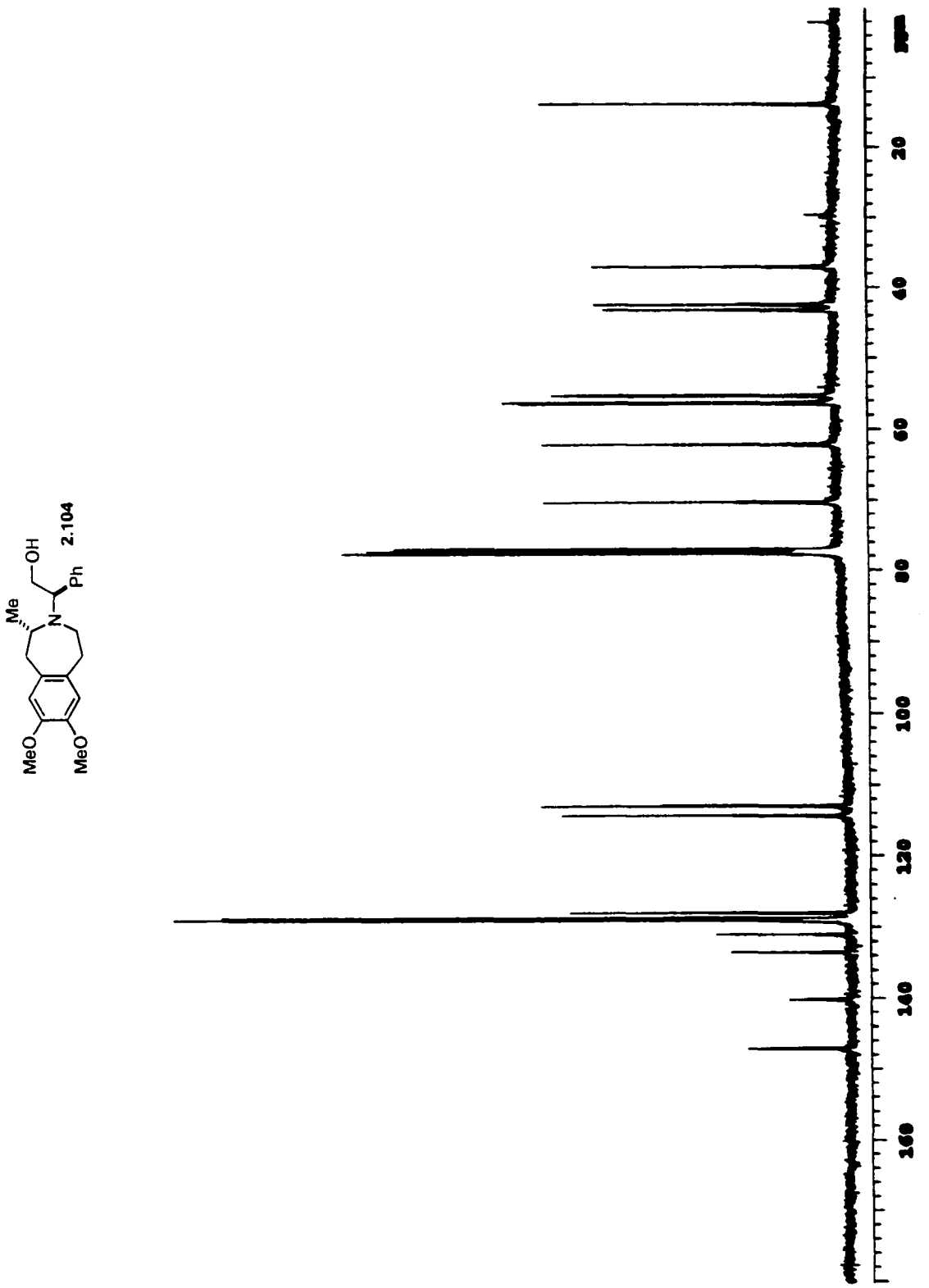


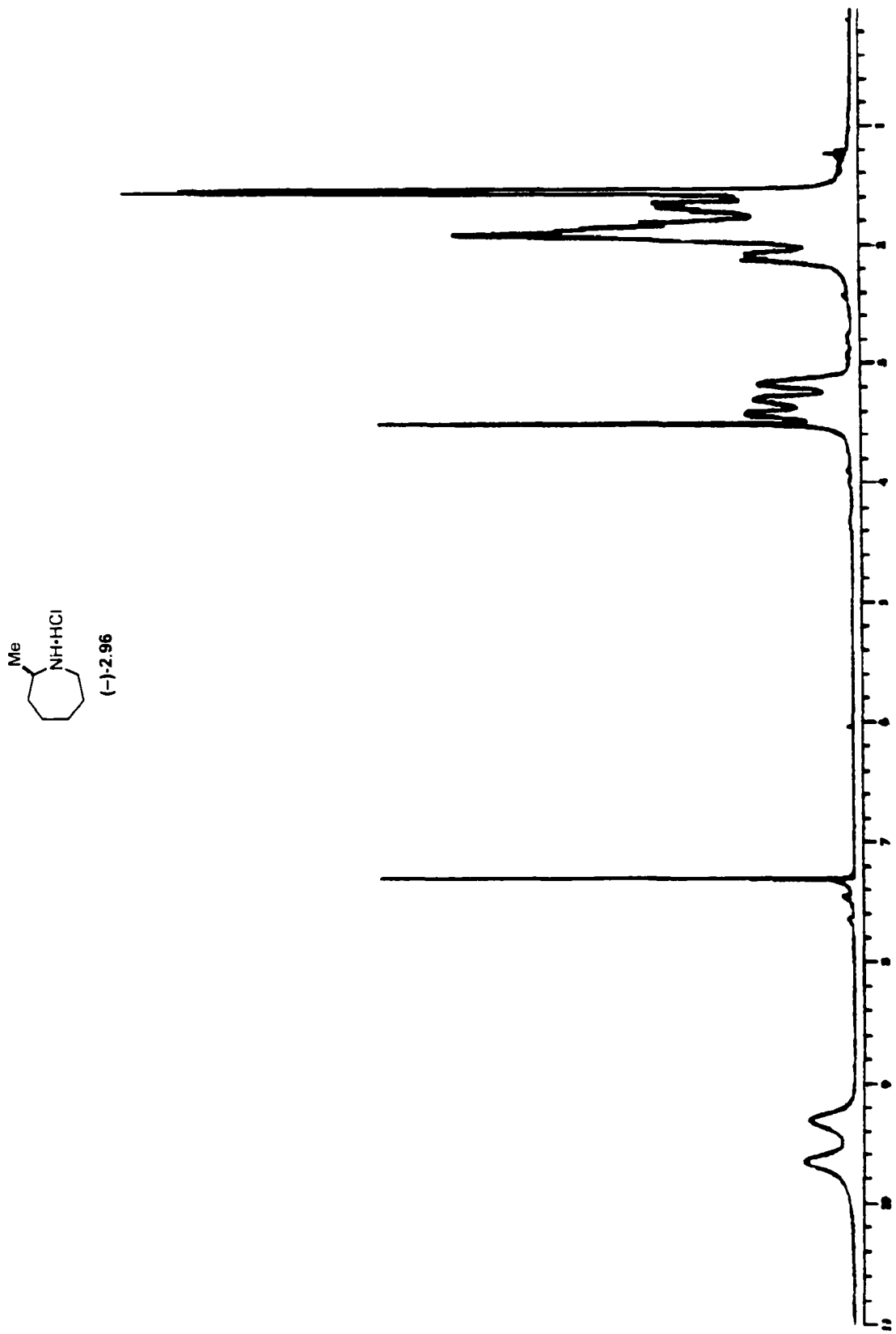




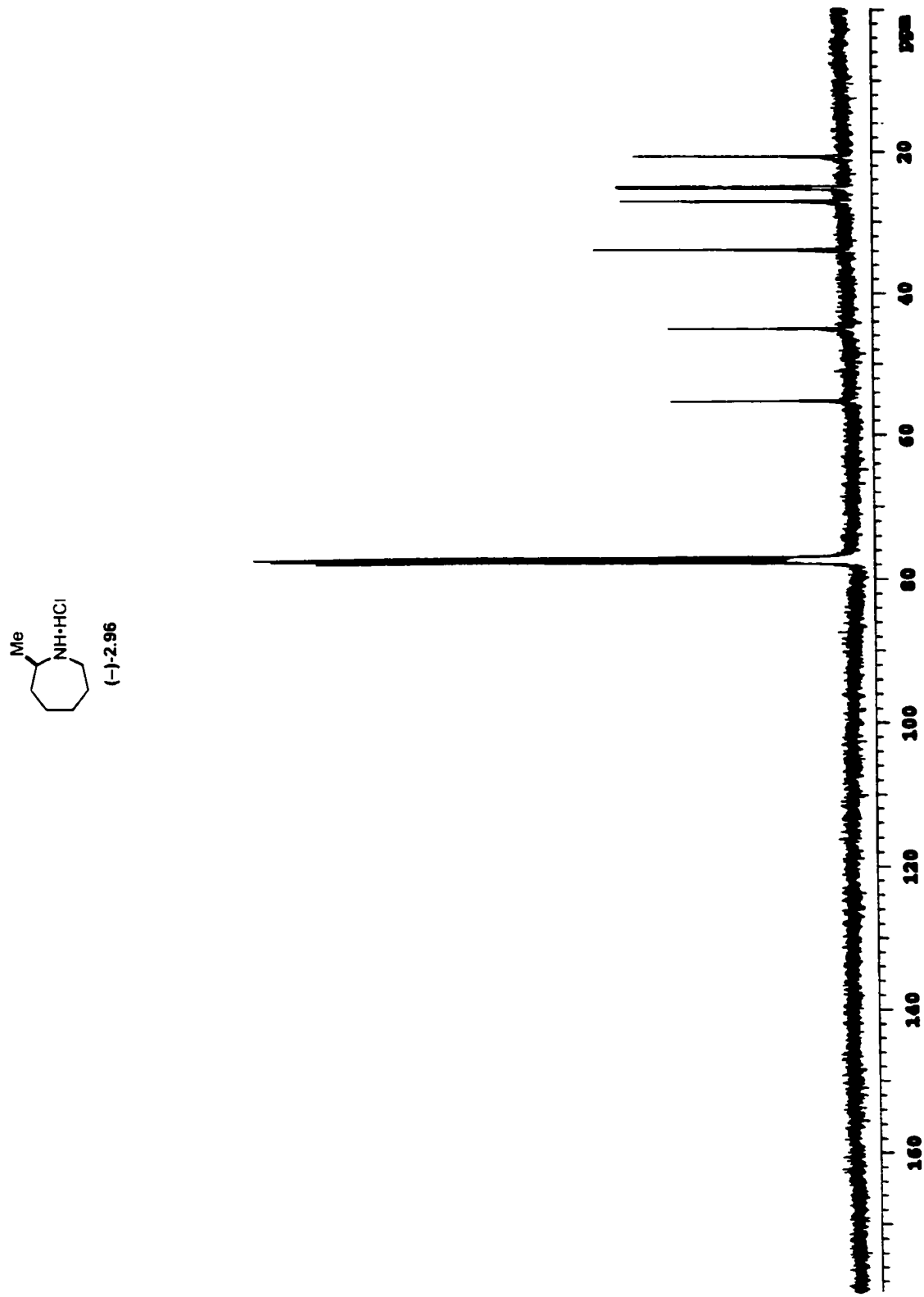


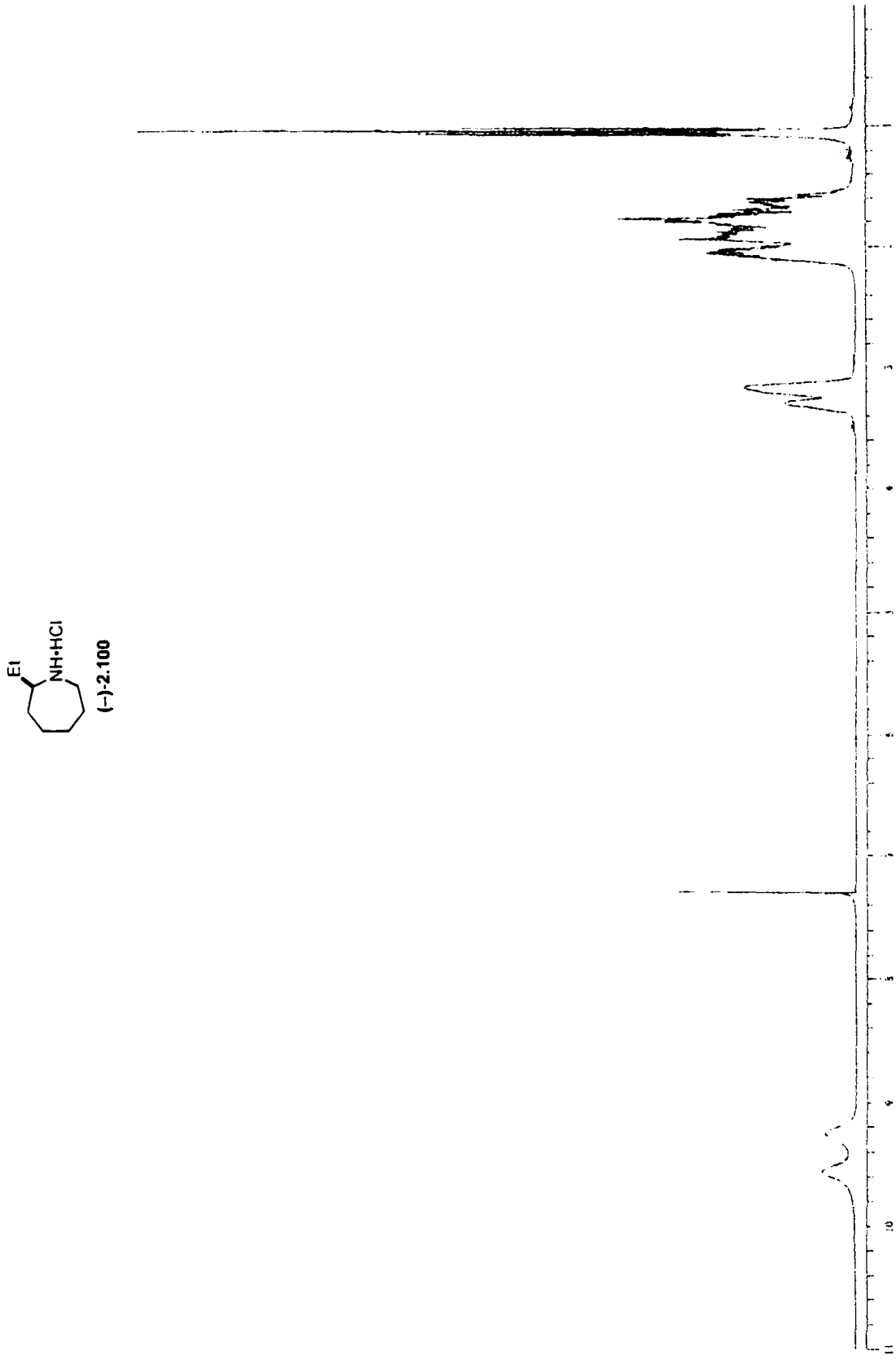


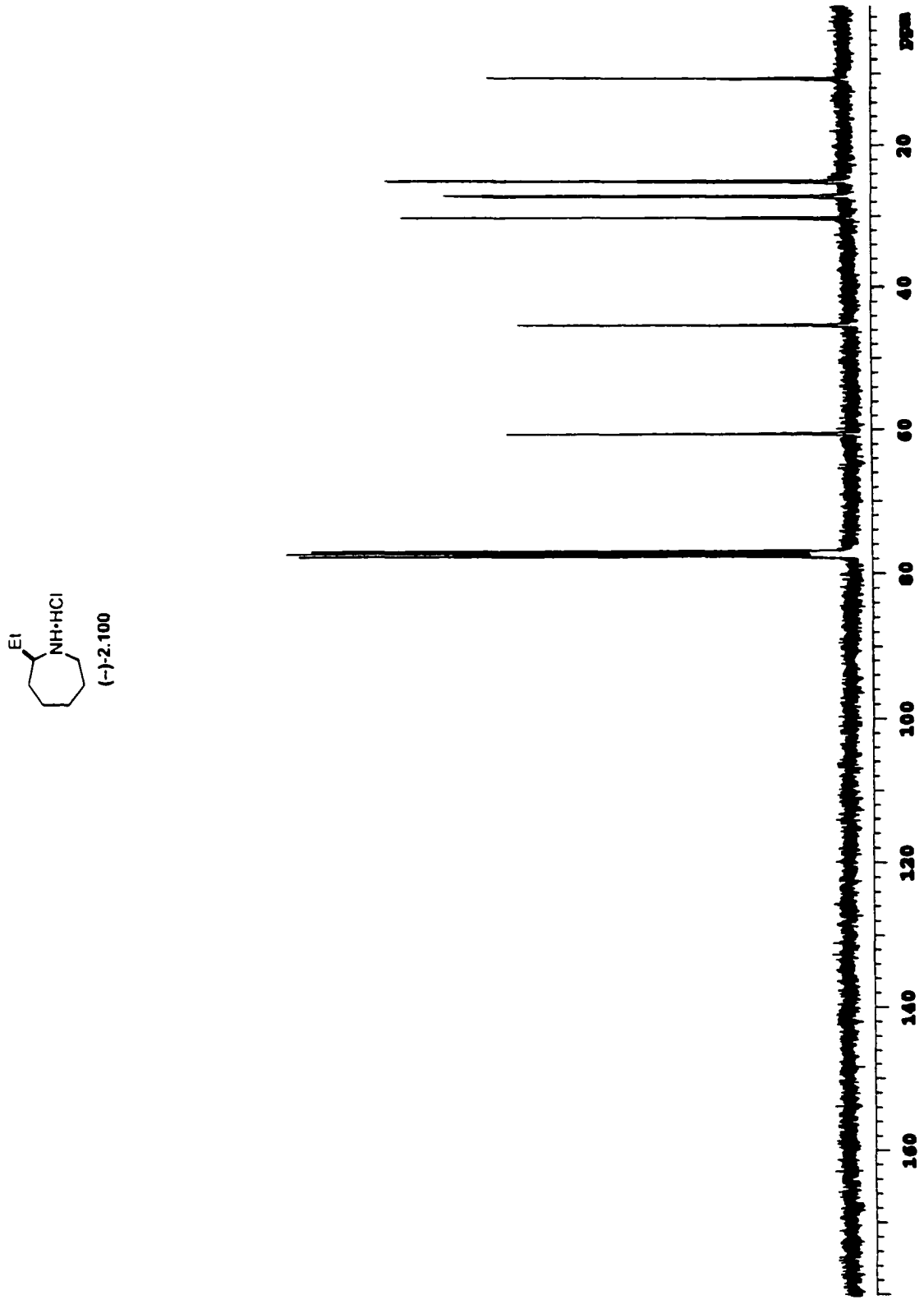


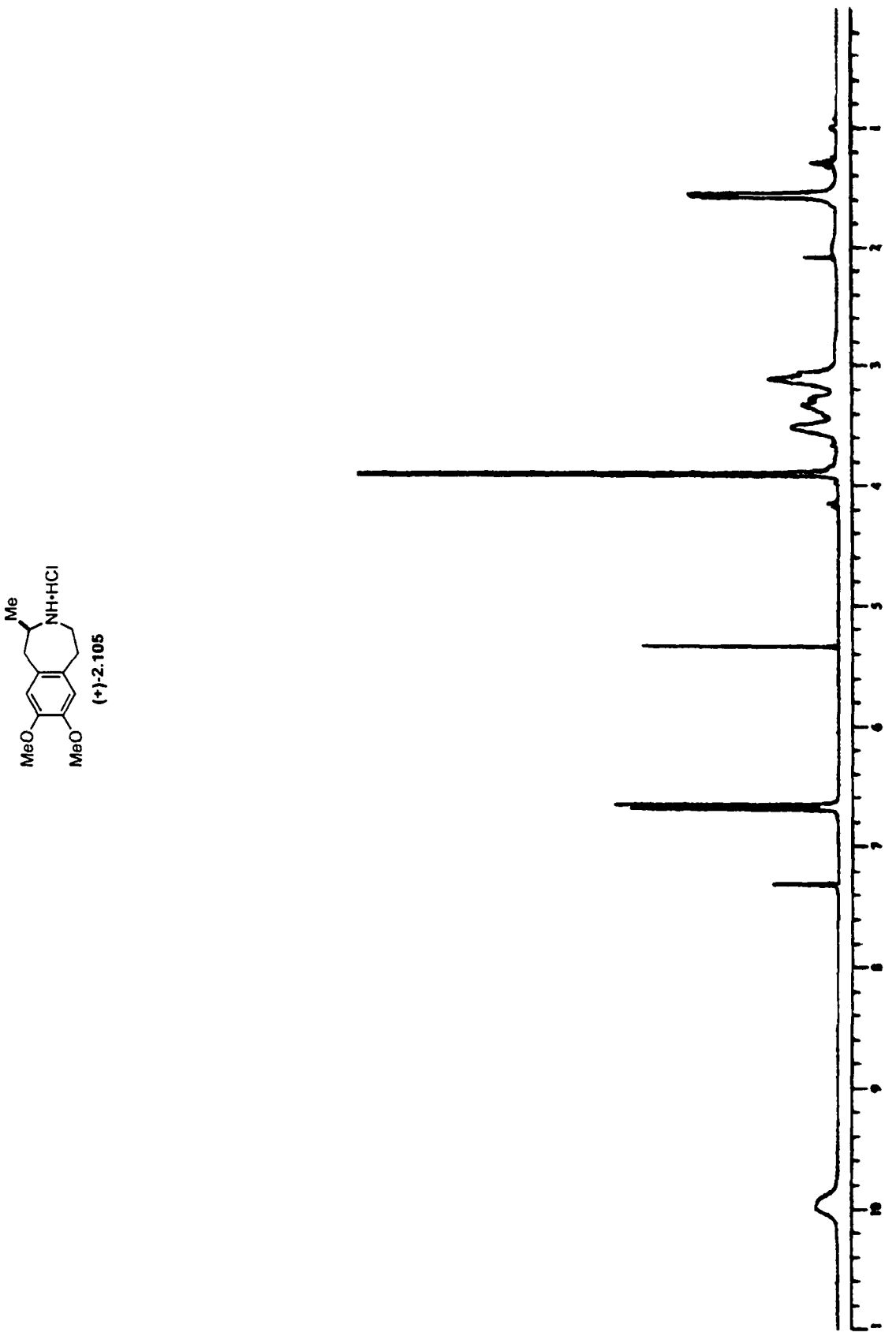


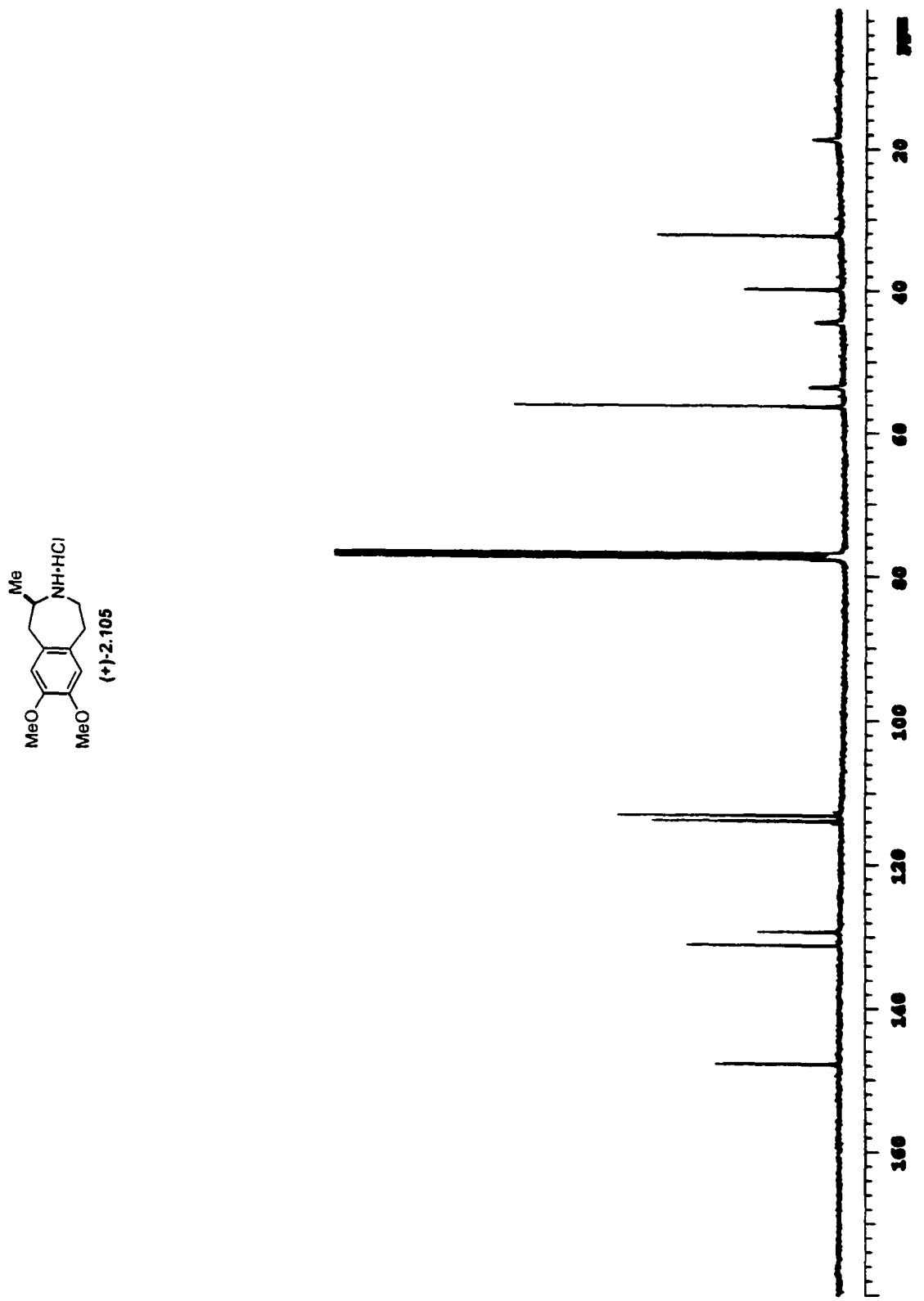
(–)-2.96

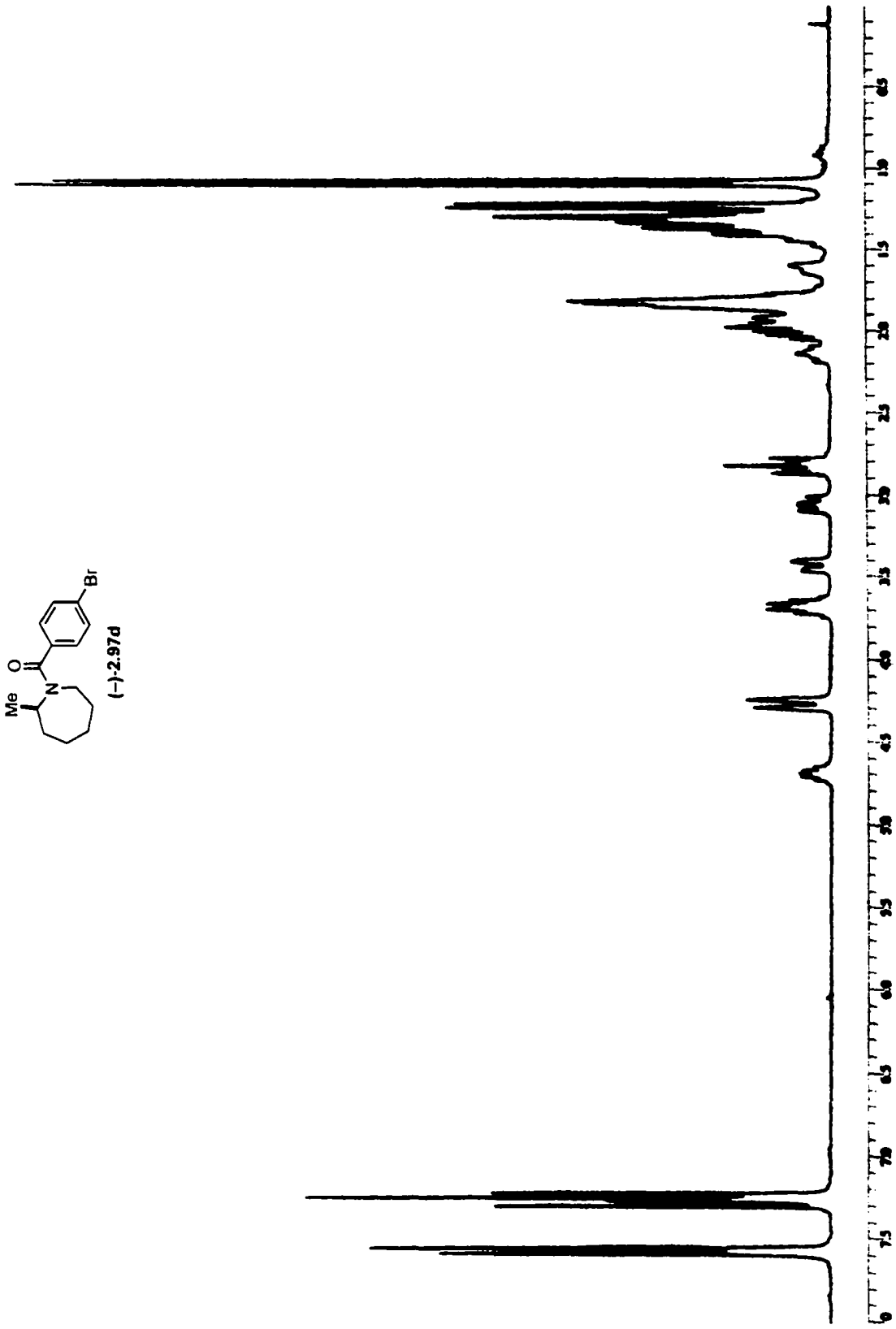


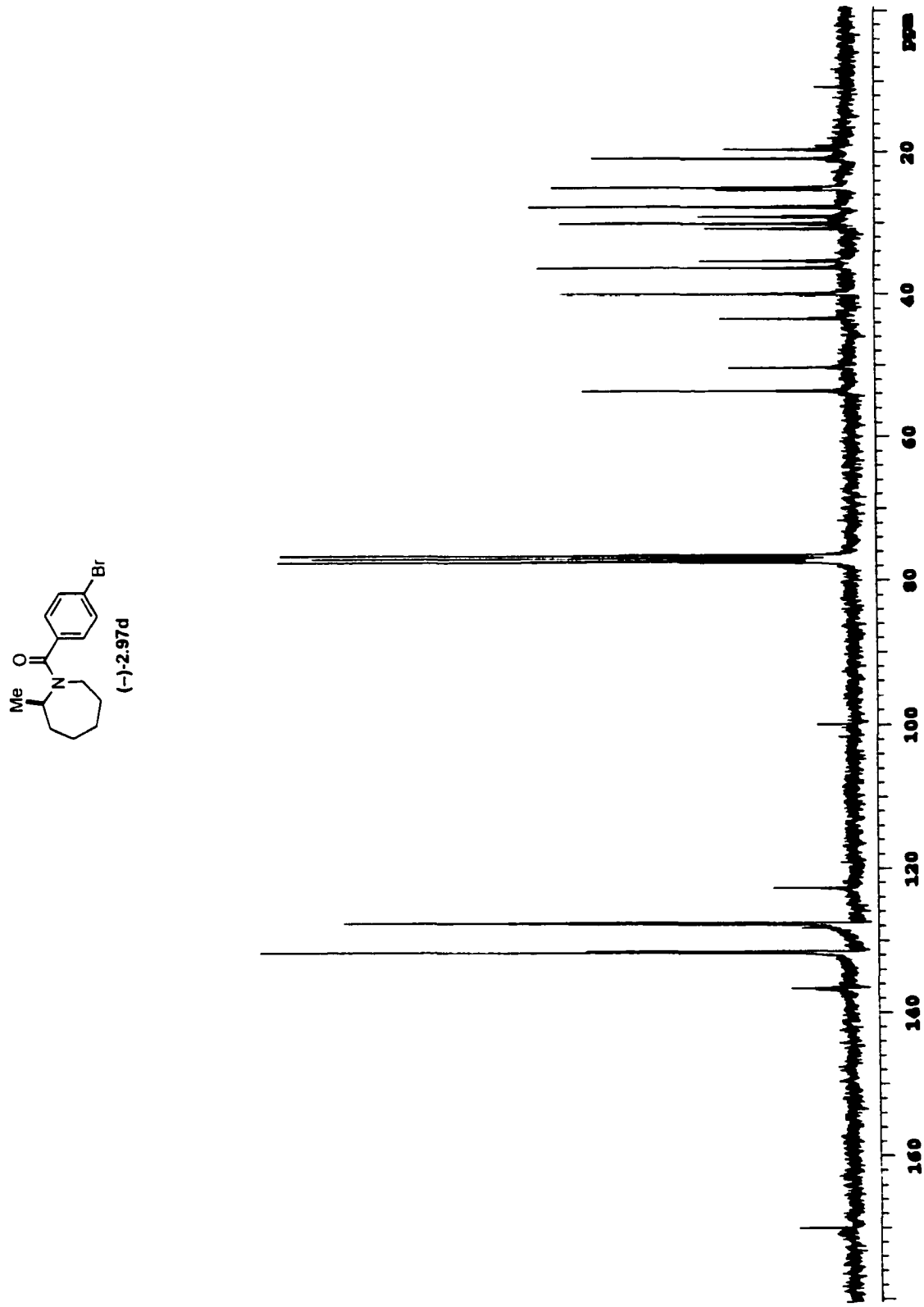


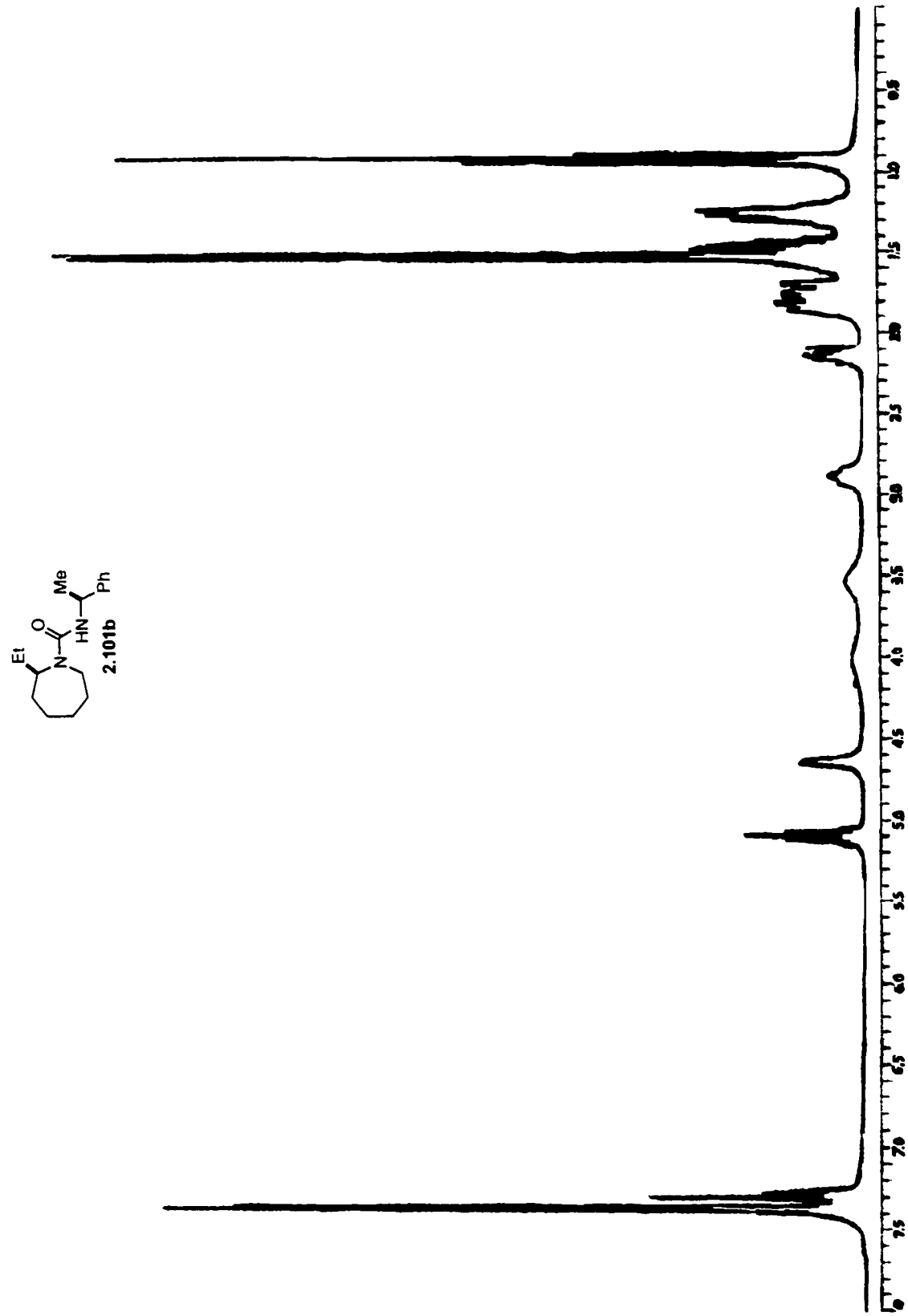


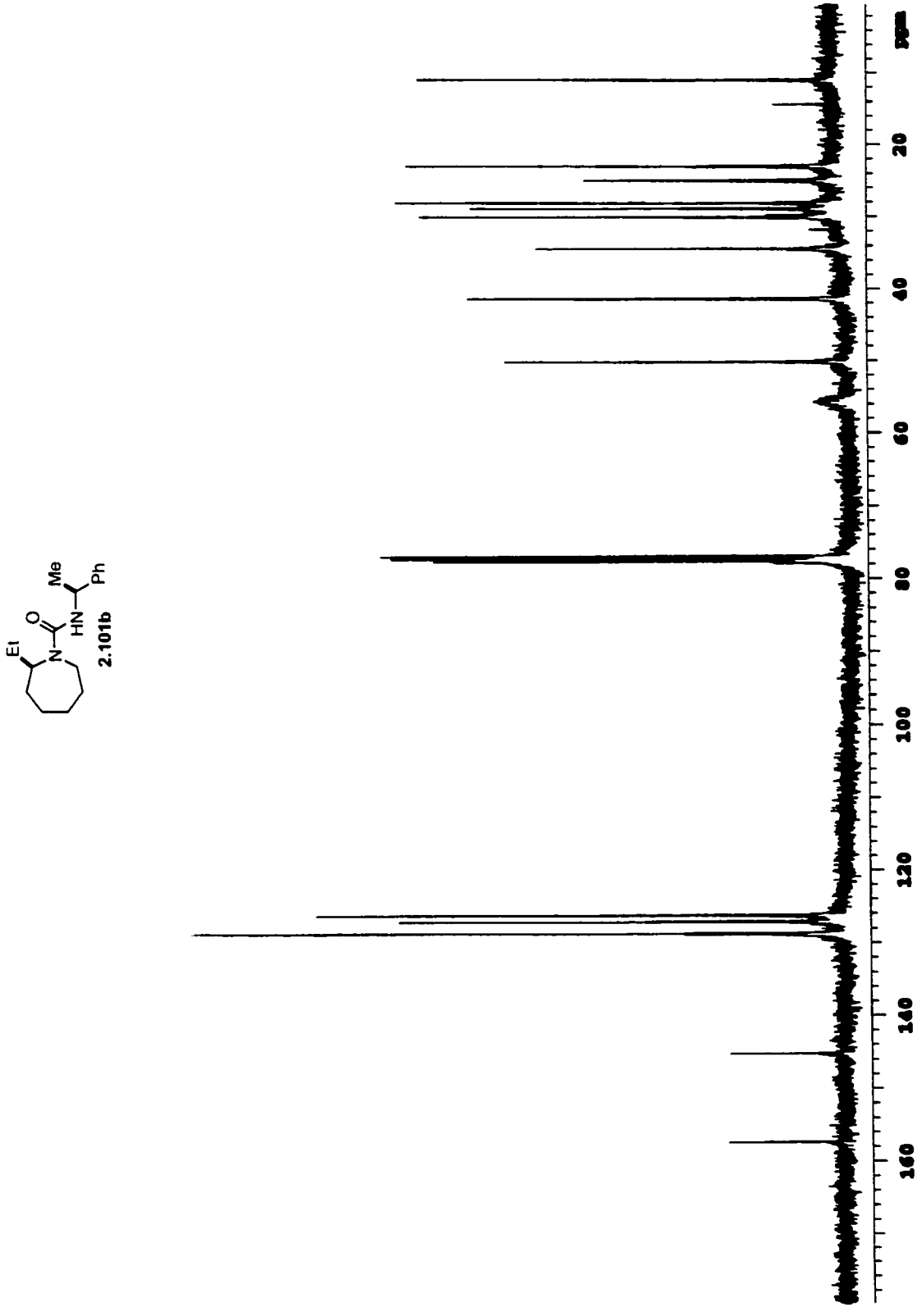


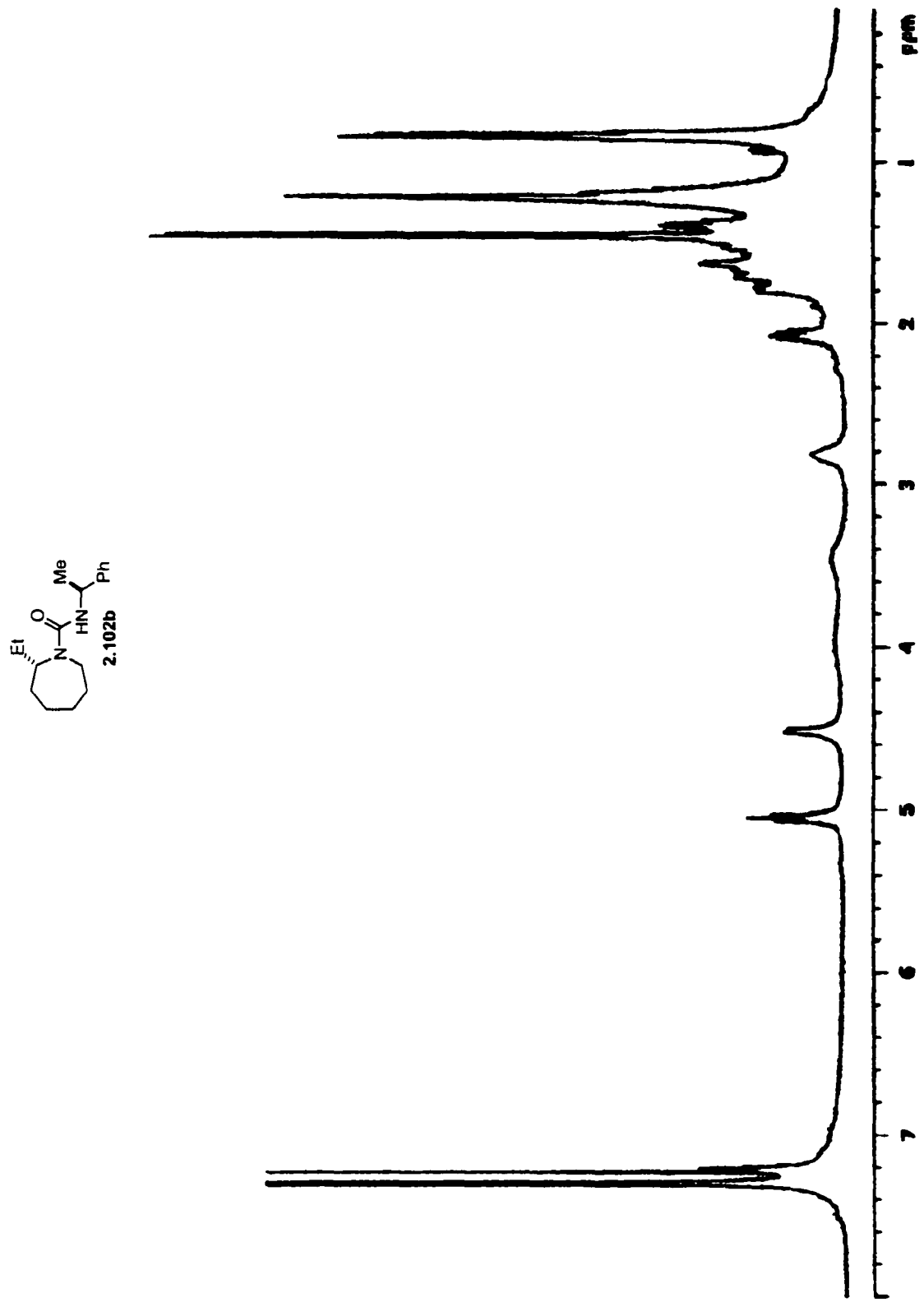


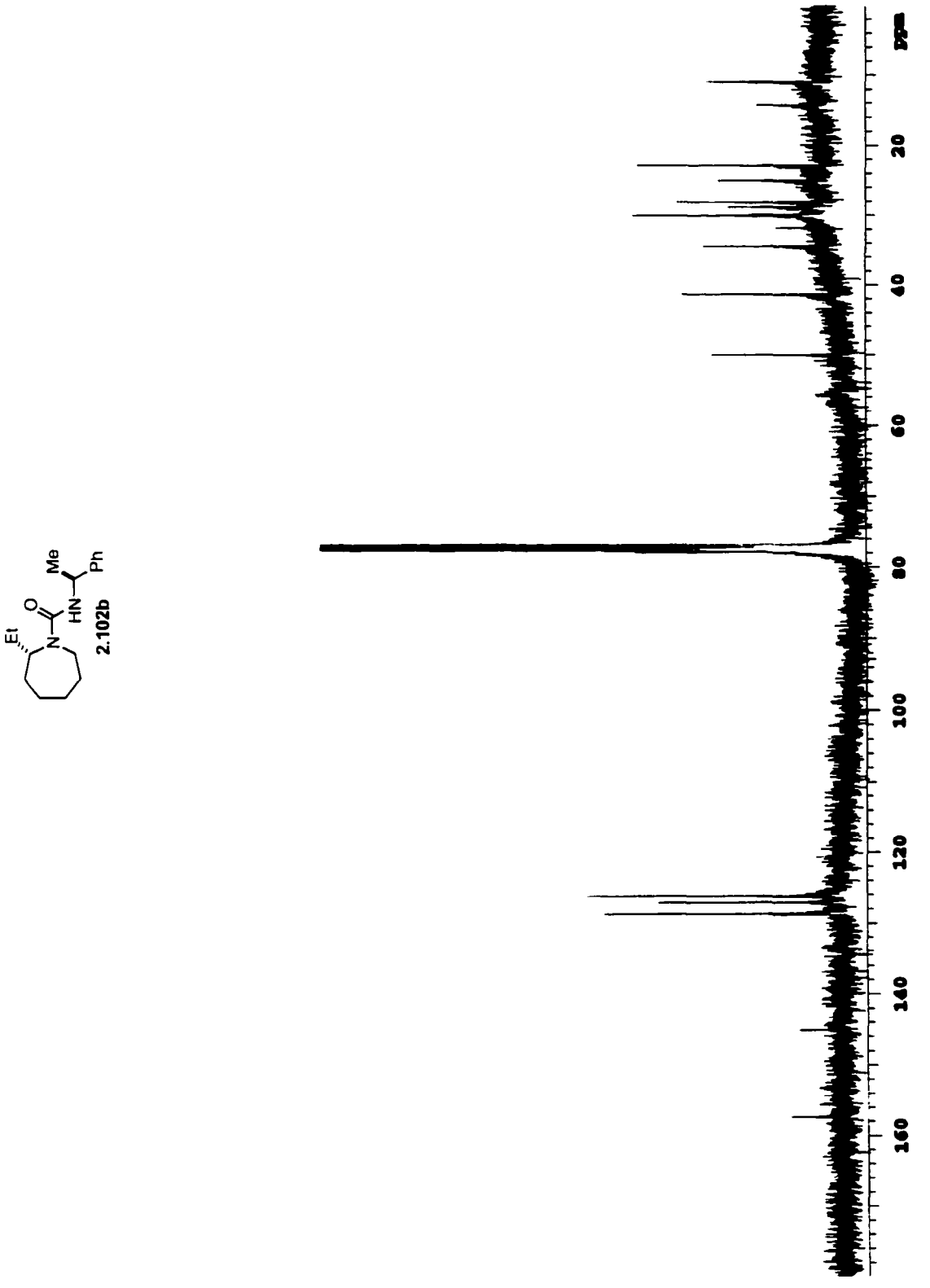


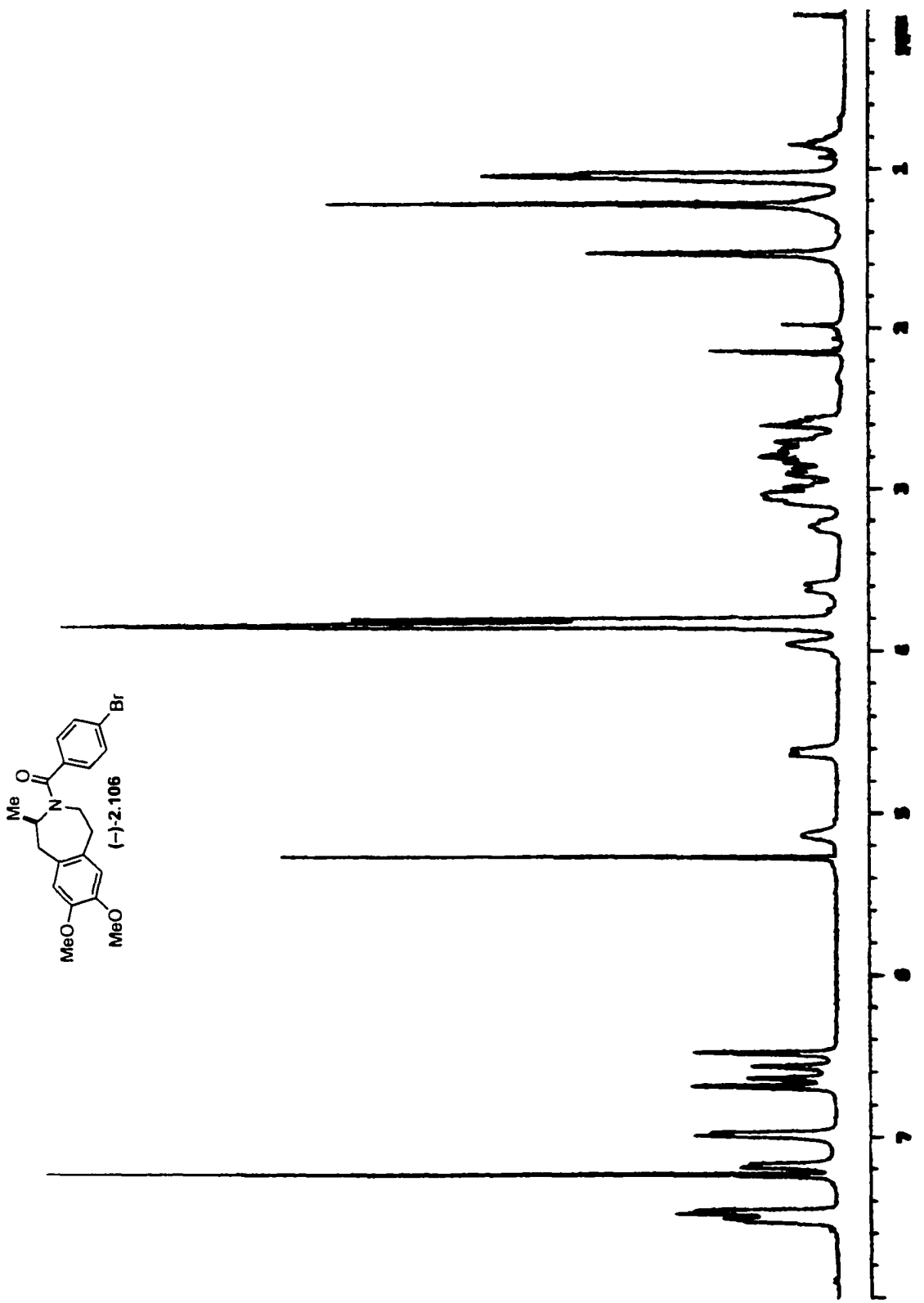


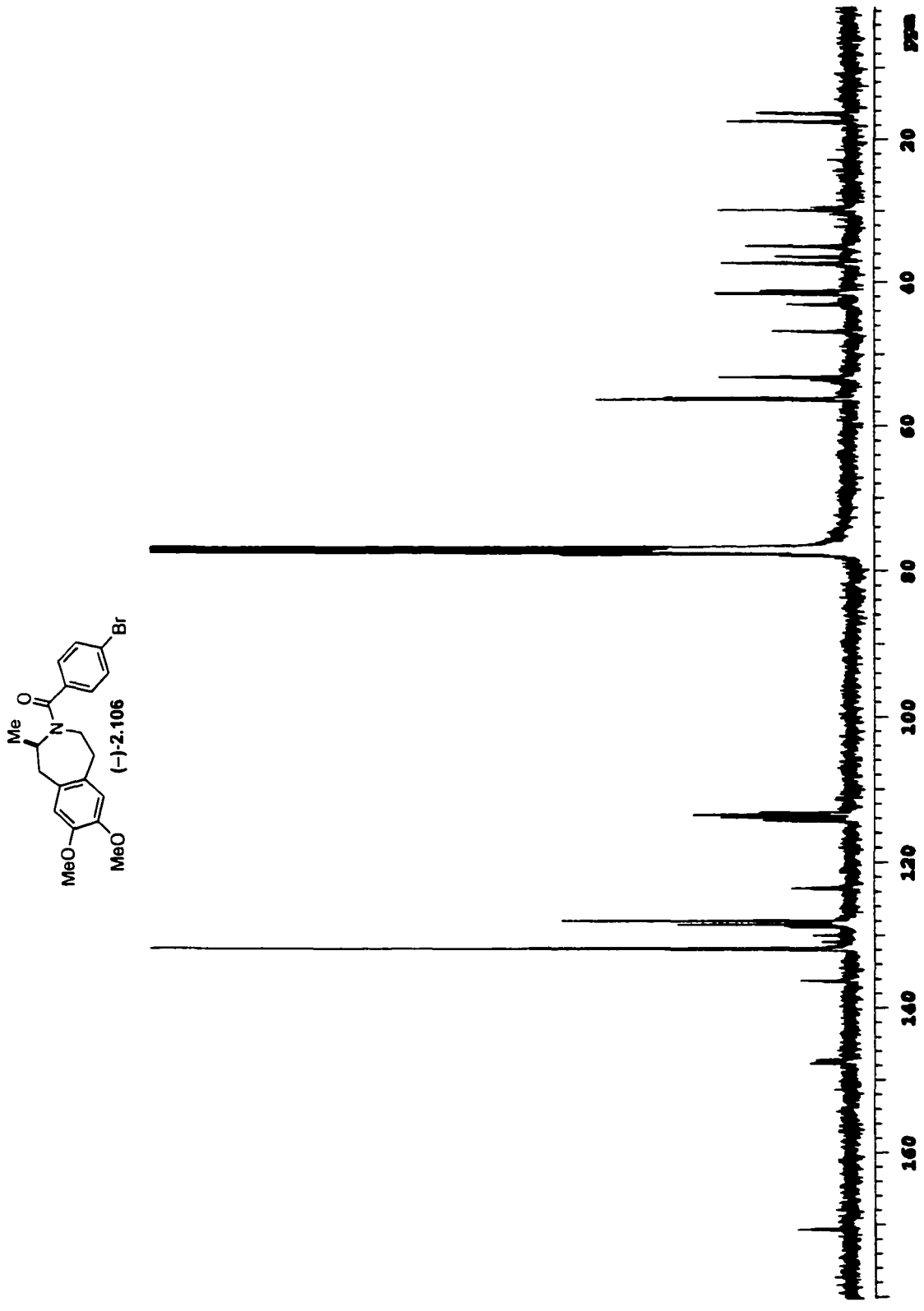


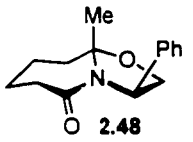




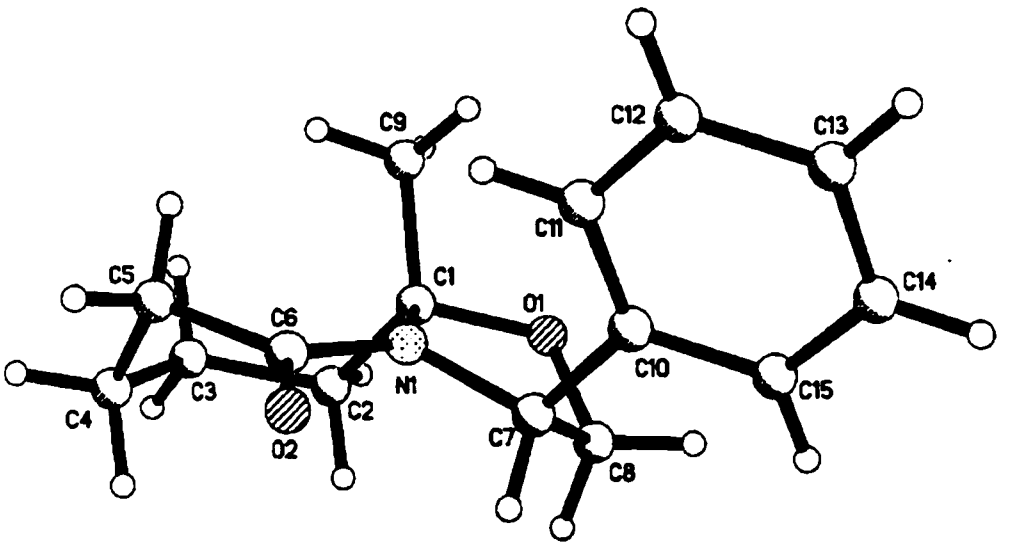








2.48



Pages 178-183

Table 1. Crystal data and structure refinement for 1.

Identification code	amccd22 SVD701TOP Downing/Meyers
Empirical formula	$C_{15}H_{19}NO_2$
Formula weight	245.31
Temperature	167(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.0338(2) Å alpha = 90° b = 10.2400(2) Å beta = 90° c = 15.93020(10) Å gamma = 90°
Volume, Z	1310.52(4) $Å^3$, 4
Density (calculated)	1.243 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	528
Crystal size	0.08 x 0.24 x 0.25 mm
θ range for data collection	2.36 to 28.44°
Limiting indices	$-10 \le h \le 10$, $-13 \le k \le 12$, $-13 \le l \le 20$
Reflections collected	8852
Independent reflections	3191 (R_{int} = 0.0427)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3191 / 0 / 163
Goodness-of-fit on F^2	1.017
Final R indices [I>2σ(I)]	R1 = 0.0450, wR2 = 0.0881
R indices (all data)	R1 = 0.0717, wR2 = 0.0987
Largest diff. peak and hole	0.143 and -0.203 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	8690(1)	5364(1)	8021(1)	31(1)
O(2)	5763(2)	8234(1)	6505(1)	44(1)
N(1)	7557(2)	6978(1)	7227(1)	26(1)
C(1)	9138(2)	6245(2)	7359(1)	27(1)
C(2)	9625(2)	5443(2)	6587(1)	36(1)
C(3)	10328(3)	6190(2)	5837(1)	46(1)
C(4)	9122(3)	7123(2)	5419(1)	45(1)
C(5)	8538(2)	8236(2)	5990(1)	36(1)
C(6)	7197(2)	7825(2)	6591(1)	30(1)
C(7)	6194(2)	6429(2)	7726(1)	27(1)
C(8)	6944(2)	5114(2)	7974(1)	32(1)
C(9)	10542(2)	7056(2)	7711(1)	39(1)
C(10)	5636(2)	7278(2)	8453(1)	26(1)
C(11)	6061(2)	8589(2)	8516(1)	28(1)
C(12)	5459(2)	9363(2)	9167(1)	34(1)
C(13)	4418(2)	8826(2)	9768(1)	41(1)
C(14)	3970(3)	7532(2)	9706(1)	47(1)
C(15)	4567(2)	6764(2)	9059(1)	39(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(8)	1.428(2)	O(1)-C(1)	1.434(2)
O(2)-C(6)	1.233(2)	N(1)-C(6)	1.365(2)
N(1)-C(7)	1.464(2)	N(1)-C(1)	1.490(2)
C(1)-C(9)	1.509(2)	C(1)-C(2)	1.529(2)
C(2)-C(3)	1.527(3)	C(3)-C(4)	1.516(3)
C(4)-C(5)	1.532(2)	C(5)-C(6)	1.502(2)
C(7)-C(10)	1.517(2)	C(7)-C(8)	1.528(2)
C(10)-C(11)	1.389(2)	C(10)-C(15)	1.394(2)
C(11)-C(12)	1.392(2)	C(12)-C(13)	1.385(3)
C(13)-C(14)	1.377(3)	C(14)-C(15)	1.383(3)

C(8)-O(1)-C(1)	108.71(12)	C(6)-N(1)-C(7)	119.22(13)
C(6)-N(1)-C(1)	127.19(13)	C(7)-N(1)-C(1)	111.60(12)
O(1)-C(1)-N(1)	101.90(12)	O(1)-C(1)-C(9)	105.09(13)
N(1)-C(1)-C(9)	114.37(13)	O(1)-C(1)-C(2)	108.49(12)
N(1)-C(1)-C(2)	112.07(13)	C(9)-C(1)-C(2)	113.78(14)
C(3)-C(2)-C(1)	117.0(2)	C(4)-C(3)-C(2)	115.0(2)
C(3)-C(4)-C(5)	113.8(2)	C(6)-C(5)-C(4)	112.9(2)
O(2)-C(6)-N(1)	119.7(2)	O(2)-C(6)-C(5)	120.2(2)
N(1)-C(6)-C(5)	120.0(2)	N(1)-C(7)-C(10)	114.54(13)
N(1)-C(7)-C(8)	100.56(13)	C(10)-C(7)-C(8)	115.11(14)
O(1)-C(8)-C(7)	104.07(13)	C(11)-C(10)-C(15)	117.8(2)
C(11)-C(10)-C(7)	122.4(2)	C(15)-C(10)-C(7)	119.6(2)
C(10)-C(11)-C(12)	121.2(2)	C(13)-C(12)-C(11)	119.9(2)
C(14)-C(13)-C(12)	119.3(2)	C(13)-C(14)-C(15)	120.7(2)
C(14)-C(15)-C(10)	121.0(2)		

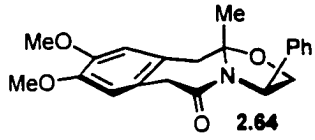
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

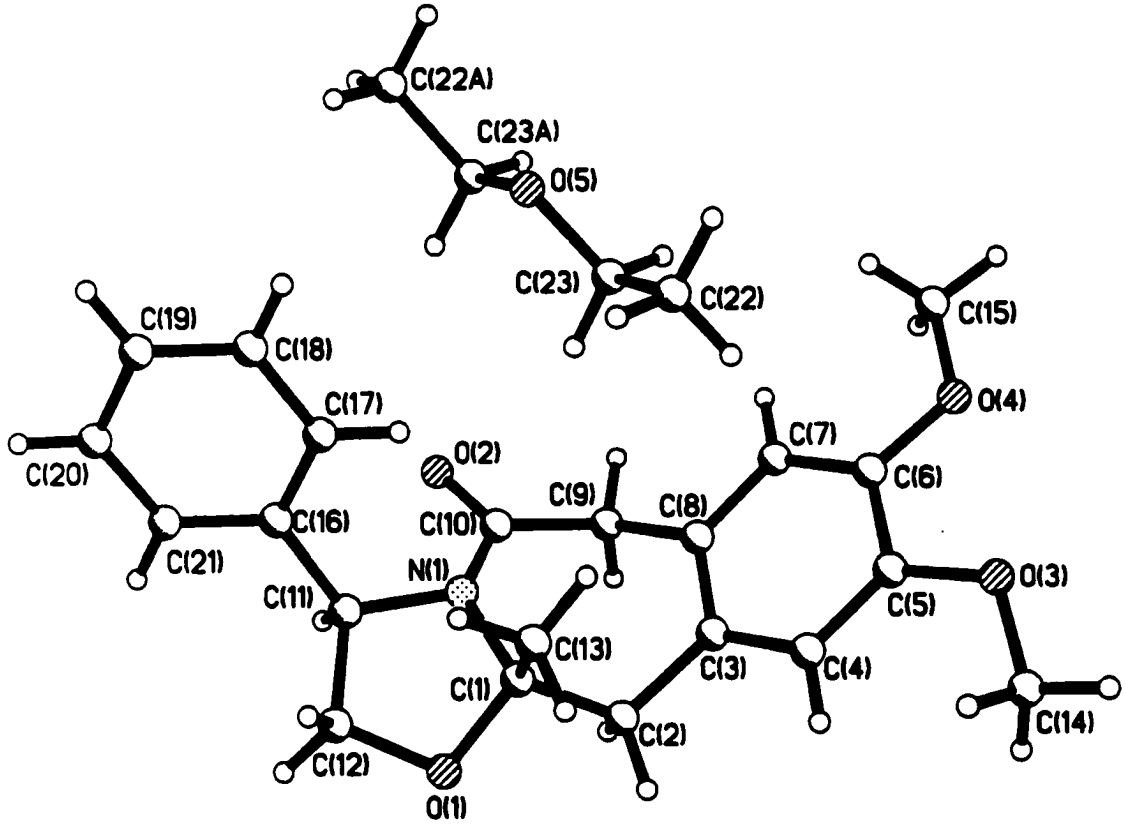
	U11	U22	U33	U23	U13	U12
O(1)	30(1)	24(1)	38(1)	7(1)	-5(1)	-2(1)
O(2)	44(1)	57(1)	30(1)	2(1)	-2(1)	26(1)
N(1)	26(1)	26(1)	25(1)	0(1)	0(1)	6(1)
C(1)	26(1)	20(1)	34(1)	4(1)	-4(1)	3(1)
C(2)	34(1)	27(1)	47(1)	-4(1)	3(1)	8(1)
C(3)	51(1)	42(1)	46(1)	-4(1)	16(1)	11(1)
C(4)	58(1)	46(1)	32(1)	0(1)	13(1)	10(1)
C(5)	49(1)	32(1)	27(1)	7(1)	4(1)	9(1)
C(6)	40(1)	28(1)	23(1)	-4(1)	-3(1)	10(1)
C(7)	24(1)	29(1)	28(1)	-2(1)	-4(1)	-2(1)
C(8)	32(1)	26(1)	40(1)	0(1)	1(1)	-5(1)
C(9)	35(1)	30(1)	51(1)	5(1)	-12(1)	-7(1)
C(10)	23(1)	30(1)	24(1)	1(1)	-4(1)	0(1)
C(11)	28(1)	31(1)	26(1)	0(1)	-1(1)	-1(1)
C(12)	39(1)	32(1)	32(1)	-5(1)	-4(1)	4(1)
C(13)	43(1)	50(1)	30(1)	-9(1)	5(1)	6(1)
C(14)	46(1)	58(1)	37(1)	2(1)	15(1)	-5(1)
C(15)	40(1)	39(1)	38(1)	-1(1)	5(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(2A)	10461(2)	4788(2)	6763(1)	43
H(2B)	8628(2)	4958(2)	6396(1)	43
H(3A)	11313(3)	6691(2)	6026(1)	56
H(3B)	10714(3)	5550(2)	5414(1)	56
H(4A)	8137(3)	6625(2)	5227(1)	54
H(4B)	9663(3)	7502(2)	4916(1)	54
H(5A)	9501(2)	8569(2)	6313(1)	43
H(5B)	8115(2)	8960(2)	5637(1)	43
H(7A)	5220(2)	6271(2)	7348(1)	32
H(8A)	6506(2)	4818(2)	8522(1)	39
H(8B)	6698(2)	4440(2)	7545(1)	39
H(9A)	10913(2)	7686(2)	7287(1)	58
H(9B)	11472(2)	6484(2)	7864(1)	58
H(9C)	10154(2)	7525(2)	8210(1)	58
H(11A)	6776(2)	8964(2)	8107(1)	34
H(12A)	5762(2)	10258(2)	9199(1)	41
H(13A)	4018(2)	9345(2)	10219(1)	50
H(14A)	3242(3)	7162(2)	10111(1)	57
H(15A)	4245(2)	5873(2)	9026(1)	47



2.64



Pages 184-189

Table 1. Crystal data and structure refinement for 1.

Identification code	amccd21 (Downing/Meyers)
Empirical formula	$C_{23}H_{28}NO_{4.50}$
Formula weight	390.46
Temperature	167(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12$
Unit cell dimensions	a = 13.0477(9) Å alpha = 90° b = 14.3234(10) Å beta = 90° c = 11.1515(8) Å gamma = 90°
Volume, Z	2084.1(3) $Å^3$, 4
Density (calculated)	1.244 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	836
Crystal size	0.04 x 0.26 x 0.38 mm
θ range for data collection	1.83 to 28.41°
Limiting indices	$-17 \le h \le 16$, $-19 \le k \le 15$, $-14 \le l \le 9$
Reflections collected	13826
Independent reflections	5028 (R_{int} = 0.1431)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5028 / 0 / 258
Goodness-of-fit on F^2	1.004
Final R indices [I>2σ(I)]	R1 = 0.0904, wR2 = 0.1598
R indices (all data)	R1 = 0.2289, wR2 = 0.2173
Largest diff. peak and hole	0.253 and -0.307 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	6421(3)	2348(2)	1498(4)	30(1)
O(1)	6786(2)	3893(2)	1327(3)	40(1)
O(2)	6635(2)	871(2)	877(3)	38(1)
O(3)	1474(2)	3318(2)	2171(3)	42(1)
O(4)	1478(2)	1523(2)	1964(3)	40(1)
C(1)	5955(4)	3288(3)	1629(5)	34(1)
C(2)	5100(4)	3501(3)	750(5)	36(1)
C(3)	4116(4)	2975(3)	1041(4)	29(1)
C(4)	3246(4)	3431(3)	1458(5)	35(1)
C(5)	2370(4)	2942(4)	1760(5)	35(1)
C(6)	2373(4)	1960(3)	1651(5)	31(1)
C(7)	3241(3)	1510(3)	1236(4)	32(1)
C(8)	4122(4)	2010(3)	933(5)	31(1)
C(9)	5023(4)	1505(3)	394(5)	33(1)
C(10)	6076(4)	1555(4)	963(5)	32(1)
C(11)	7529(3)	2420(3)	1726(5)	33(1)
C(12)	7689(4)	3481(3)	1831(5)	39(1)
C(13)	5622(4)	3462(4)	2935(5)	41(1)
C(14)	1437(4)	4318(3)	2212(5)	45(2)
C(15)	1476(4)	530(3)	1874(6)	46(2)
C(16)	7926(4)	1892(3)	2815(5)	32(1)
C(17)	7280(4)	1546(4)	3680(5)	45(2)
C(18)	7677(5)	1082(5)	4675(6)	61(2)
C(19)	8707(6)	978(4)	4822(6)	64(2)
C(20)	9365(4)	1333(4)	3958(6)	54(2)
C(21)	8973(4)	1783(4)	2963(6)	44(2)
O(5)	5000	0	4563(6)	70(2)
C(23)	4409(5)	631(4)	3855(6)	63(2)
C(22)	3832(7)	1295(5)	4638(8)	105(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(10)	1.360(6)	N(1)-C(11)	1.471(5)
N(1)-C(1)	1.485(6)	O(1)-C(12)	1.432(6)
O(1)-C(1)	1.428(5)	O(2)-C(10)	1.226(5)
O(3)-C(5)	1.366(6)	O(3)-C(14)	1.434(5)
O(4)-C(6)	1.370(5)	O(4)-C(15)	1.427(5)
C(1)-C(2)	1.517(7)	C(1)-C(13)	1.540(7)
C(2)-C(3)	1.524(7)	C(3)-C(4)	1.390(6)
C(3)-C(8)	1.387(6)	C(4)-C(5)	1.382(7)
C(5)-C(6)	1.412(6)	C(6)-C(7)	1.383(6)
C(7)-C(8)	1.396(6)	C(8)-C(9)	1.506(7)
C(9)-C(10)	1.515(7)	C(11)-C(16)	1.522(7)
C(11)-C(12)	1.538(6)	C(16)-C(17)	1.374(7)
C(16)-C(21)	1.386(6)	C(17)-C(18)	1.393(8)
C(18)-C(19)	1.362(8)	C(19)-C(20)	1.388(8)
C(20)-C(21)	1.382(8)	O(5)-C(23)	1.426(7)
O(5)-C(23)#1	1.426(7)	C(23)-C(22)	1.495(9)

C(10)-N(1)-C(11)	117.4(4)	C(10)-N(1)-C(1)	131.7(4)
C(11)-N(1)-C(1)	108.7(3)	C(12)-O(1)-C(1)	106.4(3)
C(5)-O(3)-C(14)	115.7(4)	C(6)-O(4)-C(15)	116.1(4)
O(1)-C(1)-N(1)	102.5(3)	O(1)-C(1)-C(2)	106.5(4)
N(1)-C(1)-C(2)	114.8(4)	O(1)-C(1)-C(13)	109.8(4)
N(1)-C(1)-C(13)	110.8(4)	C(2)-C(1)-C(13)	111.8(4)
C(1)-C(2)-C(3)	112.5(4)	C(4)-C(3)-C(8)	120.2(5)
C(4)-C(3)-C(2)	121.7(4)	C(8)-C(3)-C(2)	118.0(5)
C(5)-C(4)-C(3)	121.2(4)	O(3)-C(5)-C(4)	126.1(4)
O(3)-C(5)-C(6)	115.1(5)	C(4)-C(5)-C(6)	118.8(5)
O(4)-C(6)-C(7)	124.8(4)	O(4)-C(6)-C(5)	115.5(4)
C(7)-C(6)-C(5)	119.7(5)	C(6)-C(7)-C(8)	121.1(4)
C(3)-C(8)-C(7)	119.0(5)	C(3)-C(8)-C(9)	121.2(5)
C(7)-C(8)-C(9)	119.6(4)	C(8)-C(9)-C(10)	121.2(4)
O(2)-C(10)-N(1)	120.3(4)	O(2)-C(10)-C(9)	118.0(4)
N(1)-C(10)-C(9)	121.6(4)	N(1)-C(11)-C(16)	115.9(4)
N(1)-C(11)-C(12)	102.5(4)	C(16)-C(11)-C(12)	112.6(4)
O(1)-C(12)-C(11)	105.4(4)	C(17)-C(16)-C(21)	118.7(5)
C(17)-C(16)-C(11)	122.1(4)	C(21)-C(16)-C(11)	119.1(5)
C(16)-C(17)-C(18)	120.2(5)	C(19)-C(18)-C(17)	121.0(6)
C(18)-C(19)-C(20)	119.2(6)	C(21)-C(20)-C(19)	119.9(5)
C(20)-C(21)-C(16)	120.9(6)	C(23)-O(5)-C(23)#1	112.8(7)
O(5)-C(23)-C(22)	110.6(6)		

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,z

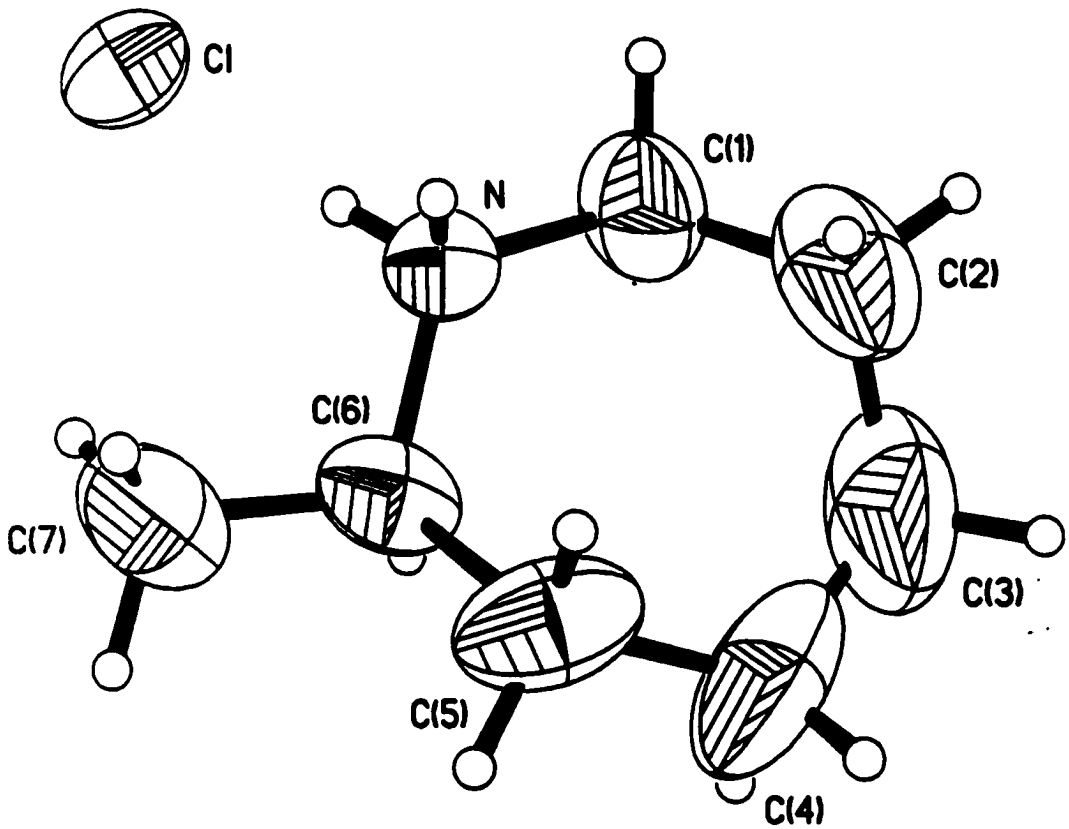
Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
N(1)	34(2)	26(2)	30(2)	-4(2)	1(2)	-3(2)
O(1)	37(2)	36(2)	47(2)	5(2)	1(2)	-7(2)
O(2)	40(2)	33(2)	40(2)	-2(2)	0(2)	3(2)
O(3)	43(2)	36(2)	46(2)	-1(2)	4(2)	12(2)
O(4)	34(2)	33(2)	52(2)	9(2)	7(2)	-1(2)
C(1)	35(3)	28(3)	39(3)	0(3)	6(3)	-5(2)
C(2)	38(3)	28(3)	40(3)	1(3)	2(3)	2(2)
C(3)	33(3)	27(3)	28(3)	2(2)	0(3)	-4(2)
C(4)	43(3)	30(3)	32(3)	1(3)	1(3)	4(3)
C(5)	40(3)	36(3)	30(3)	-2(3)	0(3)	6(2)
C(6)	35(3)	34(3)	23(3)	6(3)	-1(3)	2(2)
C(7)	35(3)	25(2)	35(3)	1(2)	-7(3)	4(2)
C(8)	35(3)	30(3)	26(3)	1(2)	-6(3)	-5(2)
C(9)	32(3)	31(3)	34(3)	1(3)	-1(3)	0(2)
C(10)	33(3)	35(3)	26(3)	1(3)	6(3)	-2(3)
C(11)	33(3)	32(3)	33(3)	-3(3)	-2(2)	0(2)
C(12)	37(3)	39(3)	41(4)	2(3)	-3(3)	-7(2)
C(13)	44(3)	43(3)	36(3)	-8(3)	5(3)	5(3)
C(14)	47(3)	40(3)	48(4)	-7(3)	2(3)	14(3)
C(15)	42(3)	33(3)	63(4)	15(3)	6(3)	-4(2)
C(16)	29(3)	31(3)	35(3)	-4(3)	-9(3)	1(2)
C(17)	37(3)	65(4)	35(3)	2(3)	-4(3)	2(3)
C(18)	62(4)	72(5)	48(4)	11(4)	-18(4)	-13(4)
C(19)	90(5)	54(4)	47(4)	7(3)	-38(4)	-4(4)
C(20)	49(4)	49(4)	65(5)	-14(3)	-32(4)	0(3)
C(21)	44(3)	43(3)	44(4)	-13(3)	-12(3)	4(3)
O(5)	114(5)	58(4)	39(4)	0	0	-8(4)
C(23)	80(5)	52(4)	58(5)	2(4)	7(4)	-3(3)
C(22)	168(9)	61(5)	86(6)	-4(5)	26(6)	1(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(2A)	5327(4)	3332(3)	-69(5)	43
H(2B)	4959(4)	4180(3)	760(5)	43
H(4A)	3254(4)	4091(3)	1536(5)	42
H(7A)	3237(3)	850(3)	1155(4)	38
H(9A)	5095(4)	1731(3)	-441(5)	39
H(9B)	4835(4)	837(3)	345(5)	39
H(11A)	7903(3)	2193(3)	1000(5)	39
H(12A)	7770(4)	3667(3)	2681(5)	47
H(12B)	8306(4)	3678(3)	1381(5)	47
H(13A)	5051(4)	3046(4)	3136(5)	61
H(13B)	5404(4)	4112(4)	3026(5)	61
H(13C)	6200(4)	3337(4)	3473(5)	61
H(14A)	767(4)	4518(3)	2515(5)	68
H(14B)	1542(4)	4570(3)	1404(5)	68
H(14C)	1977(4)	4549(3)	2746(5)	68
H(15A)	804(4)	289(3)	2118(6)	69
H(15B)	2007(4)	271(3)	2399(6)	69
H(15C)	1614(4)	347(3)	1043(6)	69
H(17A)	6560(4)	1623(4)	3600(5)	55
H(18A)	7223(5)	834(5)	5260(6)	73
H(19A)	8971(6)	667(4)	5508(6)	76
H(20A)	10086(4)	1267(4)	4051(6)	65
H(21A)	9428(4)	2021(4)	2372(6)	53
H(23A)	3921(5)	274(4)	3353(6)	76
H(23B)	4869(5)	985(4)	3315(6)	76
H(22A)	3431(7)	1722(5)	4137(8)	158
H(22B)	4316(7)	1654(5)	5126(8)	158
H(22C)	3370(7)	944(5)	5165(8)	158

(–)-2.96



Pages 190-196

Table 1. Crystal data and structure refinement for 1.

Identification code	sadam23a
Empirical formula	$C_7H_{16}ClN$
Formula weight	149.66
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 7.4172(12) Å alpha = 90.000(4)°
	b = 7.3943(11) Å beta = 93.570(3)°
	c = 8.1849(13) Å gamma = 90.000(3)°
Volume, Z	448.03(12) $Å^3$, 2
Density (calculated)	1.109 Mg/m^3
Absorption coefficient	0.352 mm^{-1}
Absorption correction	SADABS
Transmission factors	0.809 - 0.978
F(000)	164
Crystal size	0.42 x 0.13 x 0.03 mm
θ range for data collection	2.49 to 28.19°
Limiting indices	$-9 \le h \le 9$, $-8 \le k \le 8$, $-10 \le l \le 6$
Reflections collected	2300
Independent reflections	1814 (R_{int} = 0.0615)
Completeness to θ = 28.19°	91.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1814 / 1 / 84
Goodness-of-fit on F^2	1.011
Final R indices [I>2σ(I)]	R1 = 0.0764, wR2 = 0.1228
R indices (all data)	R1 = 0.2006, wR2 = 0.1488

Absolute structure parameter	0.00(19)
Extinction coefficient	0.030(8)
Largest diff. peak and hole	0.199 and -0.170 $e\text{Å}^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cl	-6549(2)	4179(1)	-1610(2)	66(1)
N	-3773(6)	3396(6)	1360(5)	52(1)
C(1)	-4678(8)	4090(13)	2803(7)	82(2)
C(2)	-3663(12)	3727(12)	4432(9)	107(3)
C(3)	-2053(15)	4975(14)	4764(11)	141(4)
C(4)	-450(14)	4776(12)	3855(11)	126(4)
C(5)	-514(8)	3647(9)	2324(9)	87(3)
C(6)	-1990(7)	4140(12)	980(7)	61(2)
C(7)	-1564(8)	3461(11)	-687(9)	89(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

N-C(6)	1.483(6)	N-C(1)	1.487(7)
C(1)-C(2)	1.514(8)	C(2)-C(3)	1.520(11)
C(3)-C(4)	1.449(11)	C(4)-C(5)	1.504(10)
C(5)-C(6)	1.547(7)	C(6)-C(7)	1.505(8)
C(6)-N-C(1)	119.4(5)	N-C(1)-C(2)	114.5(6)
C(1)-C(2)-C(3)	113.1(8)	C(4)-C(3)-C(2)	120.4(8)
C(3)-C(4)-C(5)	120.0(8)	C(4)-C(5)-C(6)	116.5(6)
N-C(6)-C(7)	107.8(6)	N-C(6)-C(5)	111.4(5)
C(7)-C(6)-C(5)	112.7(6)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Cl	67(1)	45(1)	82(1)	-6(1)	-8(1)	2(1)
N	52(3)	47(3)	57(3)	-1(3)	3(3)	1(3)
C(1)	84(4)	88(5)	75(4)	-15(7)	21(4)	16(7)
C(2)	165(8)	73(8)	88(6)	5(5)	36(6)	-10(6)
C(3)	218(13)	135(10)	73(7)	-30(6)	29(7)	-30(9)
C(4)	166(10)	113(10)	91(7)	-27(6)	-45(7)	-21(7)
C(5)	63(4)	67(7)	128(7)	8(5)	-25(5)	2(4)
C(6)	57(4)	46(3)	80(4)	26(6)	7(3)	3(6)
C(7)	74(5)	109(7)	87(5)	14(5)	20(4)	2(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(0A)	-3643	2193	1487	62
H(0B)	-4533	3569	473	62
H(1A)	-5866	3545	2815	98
H(1B)	-4844	5386	2681	98
H(2C)	-3245	2484	4453	129
H(2A)	-4485	3870	5300	129
H(3A)	-2483	6204	4598	169
H(3B)	-1678	4861	5916	169
H(4B)	492	4280	4599	151
H(4C)	-65	5980	3561	151
H(5A)	-684	2394	2631	105
H(5B)	652	3732	1854	105
H(6A)	-2089	5461	929	73
H(7A)	-2536	3768	-1468	134
H(7B)	-1419	2171	-651	134
H(7C)	-467	4011	-1004	134