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A Temporary Tethering Strategy for Stereocontrol
in the Pictet-Spengler Reaction

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Stephen Herman Steffke

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William Reusch
Major professor

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A TEMPORARY TETHERING STRATEGY FOR STEREOCONTROL IN THE PICTET-SPENGLER REACTION

By

Stephen Herman Steffke

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ABSTRACT

A TEMPORARY TETHERING STRATEGY FOR STEREOCONTROL IN THE PICTET-SPENGLER REACTION

By

Stephen Herman Steffke

Recently, much attention has been directed toward the development of asymmetric versions of the Pictet-Spengler reaction, with the aim of gaining stereocontrolled entry into the C-1-substituted tetrahydroisoquinoline and tetrahydro-β-carboline ring systems. These substructures are widely distributed in natural products possessing important physiological properties. Described here is the application of a temporary tethering strategy for stereocontrol in the Pictet-Spengler reaction, that results in the asymmetric formation of 1,3-cis-disubstituted or 1,1,3-trisubstituted tetrahydro-β-carbolines from tryptophan. The carboxyl group of the aromatic amino acid functions as a tethering site, allowing the carbonyl component to be temporarily connected through an ester bond. The amino group is protected during ester formation, and its deprotection later allows the Pictet-Spengler condensation to commence. The stereocontrolled formation of a [3.3.1] bridged δ-lactone, which bears a new asymmetric center at C-1, is followed by cleavage of the lactone to give the di- or tri-substituted tetrahydro-β-carboline, that bears reactive functionality at both the C-1 and C-3 appendages that may be exploited in the synthesis of more complex alkaloids. In an effort to prepare tetrahydroisoquinolines by this method, tyrosine was also investigated as the β-arylethylamine component. Finally, an attempt to deaminate the tosylate of the bridged Pictet-Spengler product is described.

To my parents, who taught me life's most important lessons.

And to my loving wife, Beth.

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Mom and Dad, the getaways up north were of great relief and helped me through the hard times. To my entire family, thanks for the love and support.

I want to thank my wife, Beth, for helping in so many ways, and for patiently standing by me. I couldn't imagine getting through this without you. And little Emily, thanks for bringing so much happiness into our lives.

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Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
c	Concentration
Cbz	Carbobenzoxy
COSY	Correlated spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCU	1,3-Dicyclohexylurea
DEPT	Distortionless enhancement by polarization transfer
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
Et	Ethyl
Et 729	Ecteinascidin 729
Me	Methyl
MCPI	2-Chloro-1-methylpyridinium iodide
NOE	Nuclear Overhauser Effect
Ph	Phenyl

Phe	Phenylalanine
pyr	Pyridine
TEA	Triethylamine
TFA	Trifluoroacetic acid
THβC	1,2,3,4-Tetrahydro-β-carboline
THIQ	1,2,3,4-Tetrahydroisoquinoline
TLC	Thin layer chromatography
Trp	Tryptophan
Ts	*p*-Toluenesulfonyl
TsCl	*p*-Toluenesulfonyl chloride
TsOH	*p*-Toluenesulfonic acid
Tyr	Tyrosine

INTRODUCTION

The impressive structural diversity of alkaloids reflects their equally impressive range of biological properties; and the medicinal and cultural application of naturally derived alkaloids spans centuries, as well as far reaching geographical and societal boundaries.[1] Modern pharmacology continues to benefit from the exploration of traditional or folk medicine as well as from the systematic practice of isolation, characterization, and testing of newly discovered alkaloids.[2]

Given their prominent utility, the laboratory synthesis of alkaloids is frequently pursued as a source of these valuable compounds. However, it is often an intriguing structure that attracts the attention of the synthetic chemist, and the analysis of complex synthetic problems frequently inspires the creation of new methodologies, which may be broadly applicable.

The ecteinascidins (Et's) are a family of alkaloids, possessing potent antitumor activity, isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[3] The most active ecteinascidin, Et 729 (**1**), comprises only 0.00016% of the wet weight of the tunicate. Because it is highly biologically active, scarce, and has an unusual and interesting structure, Et 729 is an attractive synthetic target. Contributing to the complexity of Et 729 are the seven stereocenters, the moderately complex topology including a spiro fusion and two bridges, the high degree of functionalization, and the sheer size of the molecule.

Contemplation of Et 729 led to a highly convergent retrosynthetic strategy based mainly on topological and stereochemical concerns, and employing several hetero-keyed bond disconnections (Figure 1). The task was simplified by the identification of L-tyrosine and L-cysteine (or its synthetic equivalent L-serine) as inexpensive, chiral starting materials,

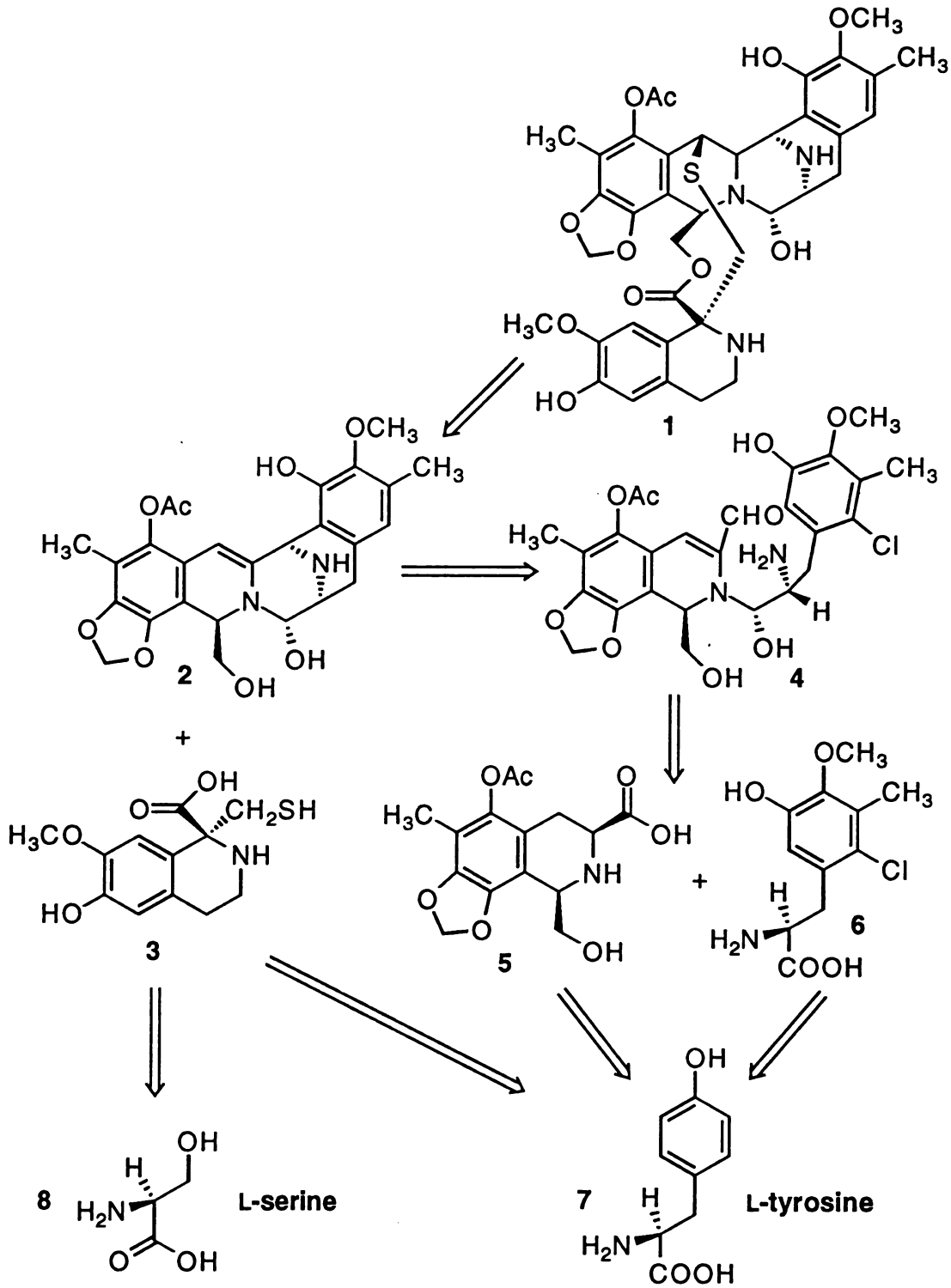


Figure 1 - Retrosynthetic Analysis of Et 729

which allowed for what Corey[4] refers to as a bidirectional search.

Pondering the execution of this scheme made it clear that the key difficulty is the introduction of the asymmetric centers in the 1,2,3,4-tetrahydroisoquinoline (THIQ) fragments **3** and **5**. The synthesis of THIQ alkaloids containing an asymmetric center at C-1 has been the subject of extensive investigation, since such alkaloids are widespread in nature and have important pharmacological properties.[5] Various approaches to the enantioselective introduction of an appendage at the 1-position of THIQ's have given satisfactory and sometimes excellent results. However, only three routes to the analogous 1-(hydroxymethyl) THIQ's have been reported. The first of these relies on the resolution of a racemic mixture to obtain the enantiomerically pure product.[7] The second is a stereoselective process that relies on the separation of a 9:1 mixture of diastereomers which after several steps yields the desired enantiomer.[8] The length of this sequence, however, results in an overall yield that is lower than that of the former process. Also, the immediate precursor of the alcohol is a 1-formyltetrahydroisoquinoline derivative, that must be used immediately upon isolation, as it is prone to racemization (75% of optical activity is lost upon chromatography on silica gel and 25% is lost during storage for 12 h in the cold). The third approach is actually a formal route based on the second, as it involves an essentially stereospecific approach to the aldehyde precursor described above.[9] While this approach could conceivably provide the enantiomerically pure THIQ fragments **3** and **5**, it is clear that a satisfactory solution has yet to be developed.

Unsatisfied with the current methodology available, we sought to devise a new procedure capable of delivering maximum stereocontrol in an efficient manner. Stereocontrol may result from steric bias, mechanistic requirements, stereoelectronic effects, or chelation control.[10] Intramolecular reactions may benefit from a powerful additional mode of control; conformational restriction. By temporarily connecting two reactants by means of a short tether, a previously intermolecular reaction can enjoy the advantages of intramolecularity. The power of this strategy is exemplified by Stork's

technology, which employs a temporary silyl tether to control the regiochemistry and stereochemistry of a variety of reactions, en route to a diverse assortment of natural products.[11]

To successfully execute any temporary tethering strategy (Figure 2), several requirements must be met. First, the reactants must contain appropriately placed functional groups that are capable of participating in tether bond formation. Second, the new connection must withstand the reaction conditions under which the intramolecular reaction occurs. Third, the system must be flexible enough to allow the reaction to proceed, yet sufficiently rigid that conformational restriction results in stereoselective bond formation. Finally, cleavage of the tether must be accomplished without affecting the remainder of the molecule.

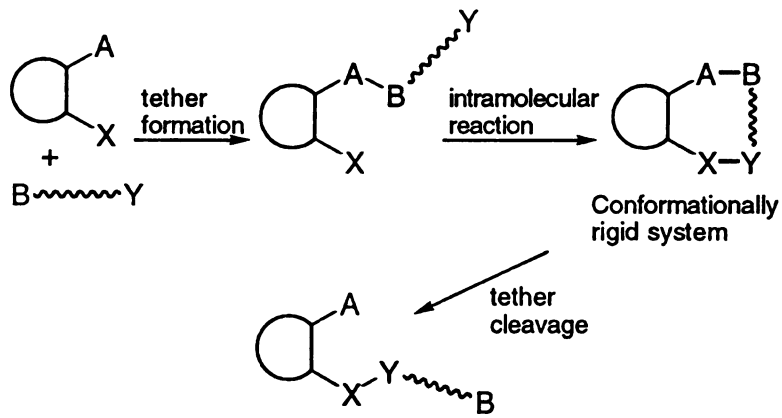


Figure 2 - Temporary Tethering Strategy

An examination of target fragment **5** suggests that these criteria can be met by the synthesis of δ-lactone **9** (Figure 3), via an intramolecular Pictet-Spengler reaction of **10**, in which the aldehyde is tethered via an ester linkage to the carboxyl group of the tyrosine derivative. Conformational restriction should be absolute, as a 1,3-diaxial relationship about the developing single atom bridge is mandatory. Likewise, one could envision the sulfur-containing target fragment **3** arising from an analogous route, generating the crucial asymmetric quaternary center with complete stereocontrol (Figure 4).

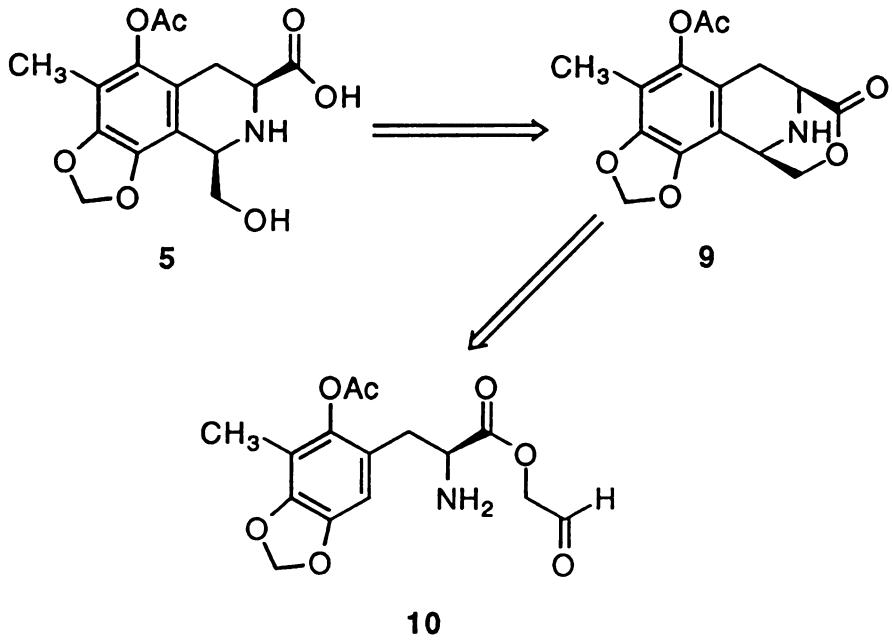


Figure 3 - Retrosynthetic Analysis of Fragment 5

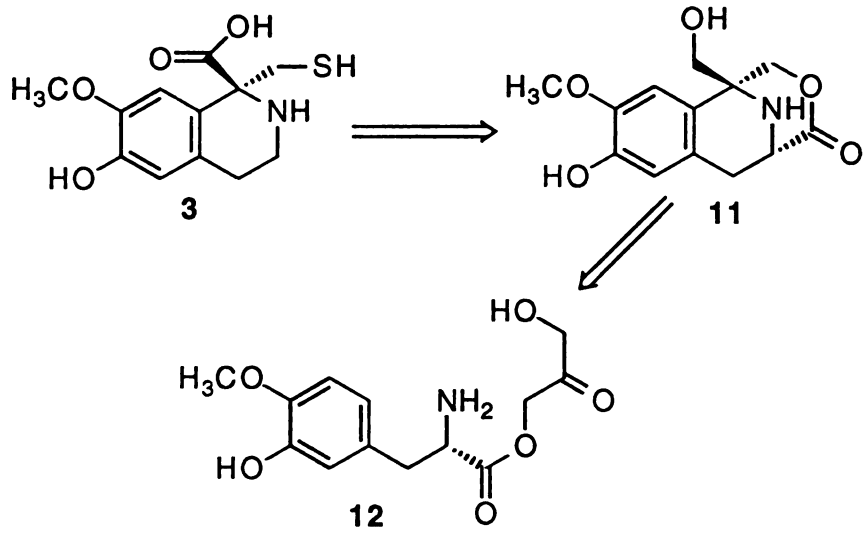


Figure 4 - Retrosynthetic Analysis of Fragment 3

A similar Pictet-Spengler reaction in which the tether is permanent has been employed by Masamune[12] in the construction of the [3.3.1] skeleton of **14** from **13** in the synthesis of ajmaline (Figure 5), suggesting that our scheme is workable. Also, Woodward[13] has demonstrated the adequacy of a bridged 1,3-diaxial lactone to temporarily create a rigid system in his classic reserpine synthesis (Figure 6). Sodium borohydride reduction of the quaternary salt **16** from the less hindered side gave **17**, with the undesired stereochemistry at position 3. Hydrolysis of both esters, followed by lactone formation, gave **18**, which is sterically congested since the 1,3-diaxial requirement of the bridged lactone rigidly fixes the cis-decalin framework, such that in the chair conformation the indole ring at C-3 must adopt an axial orientation. Acid-catalyzed epimerization at C-3 gave the more stable epimer **19**, in which the indole ring is equatorial. Cleavage of the lactone and execution of the final coupling gave reserpine **20**.

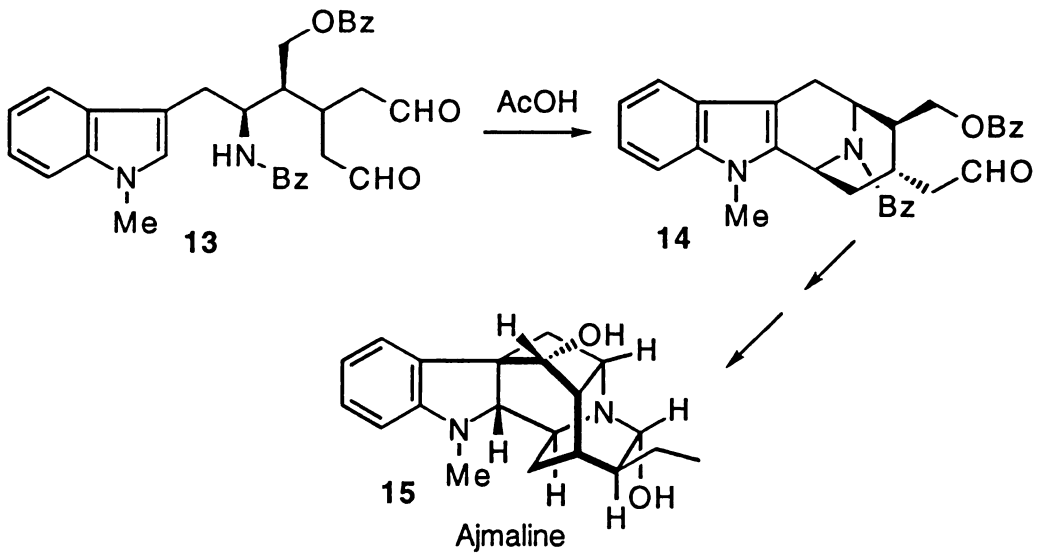


Figure 5 - Synthesis of Ajmaline

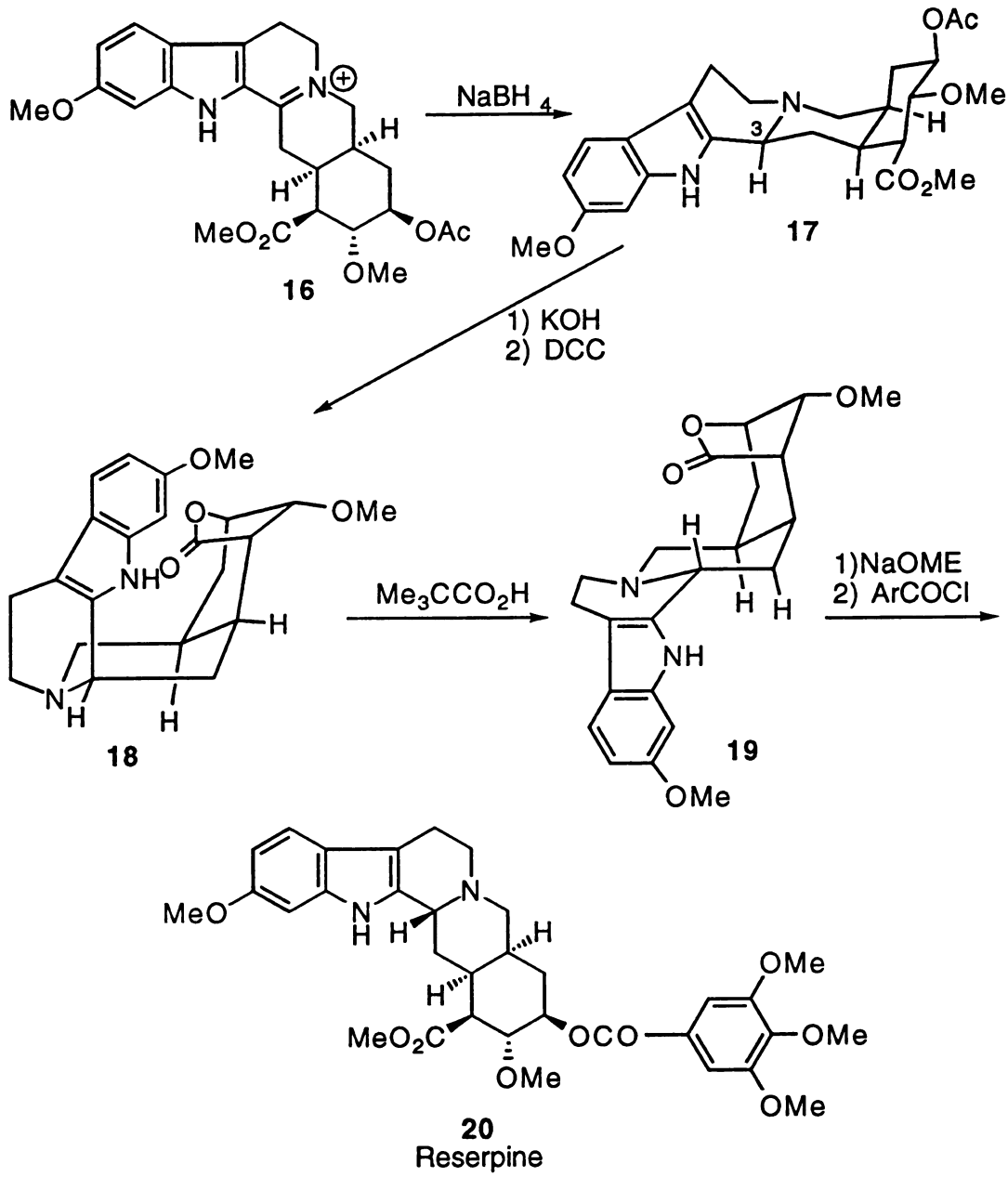
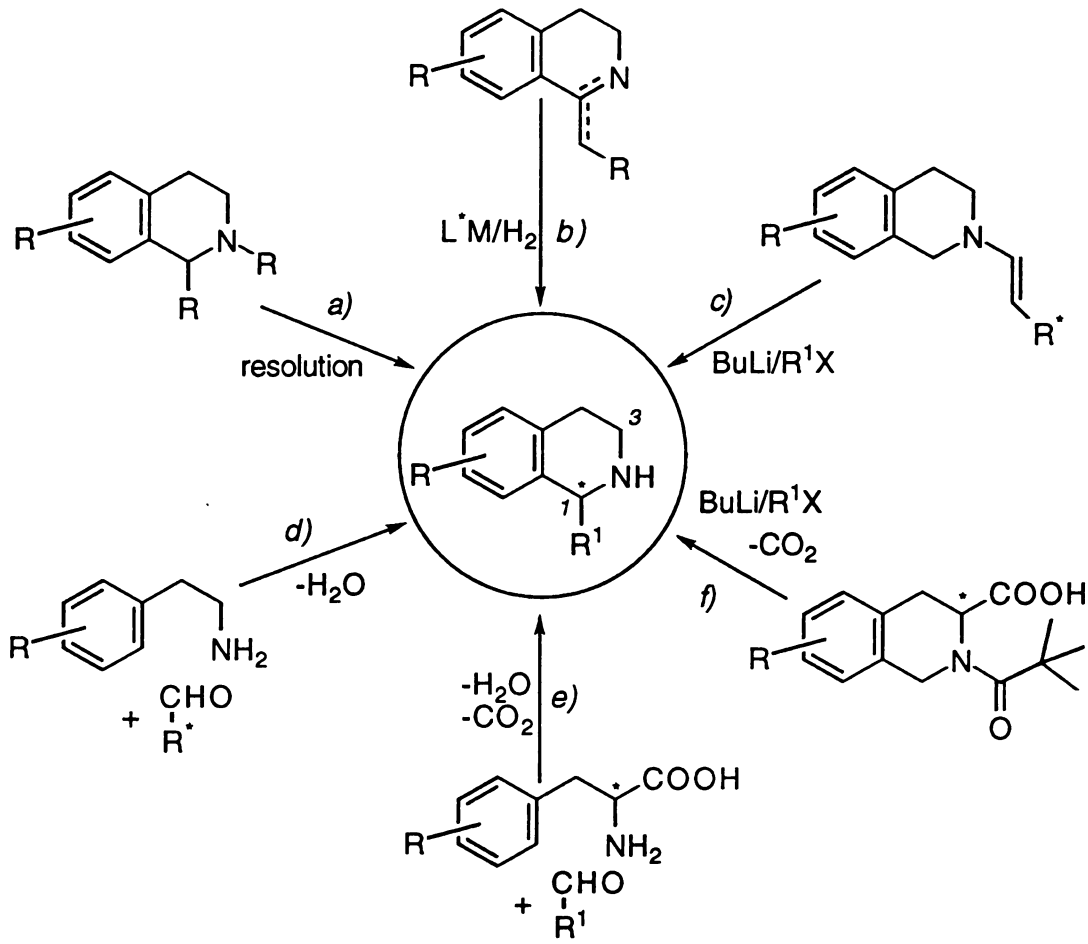


Figure 6 - Woodward's Reserpine Synthesis

Our temporary tethering strategy may be broadly applicable in the asymmetric synthesis of numerous alkaloids containing the THIQ or the 1,2,3,4-tetrahydro-β-carboline (THβC) framework. As pointed out by Seebach,[6b] all possible methods of synthesizing enantiomerically pure compounds have been applied in this vein. As shown in Figure 7, these broad categories are: *a)* resolution, *b)* catalytic and *c)* stoichiometric enantioselective reactions and *d) e) f)* the incorporation of components from the pool of chiral building blocks. Many of these methods, as well as our own, rely upon the transfer of asymmetry from C-3 to C-1, resulting in the initial formation of a 1,3-disubstituted derivative. These derivatives may themselves be desirable targets but more often function as stepping stones leading to C-1 substituted products through decarboxylation. Both classes of compounds may provide a springboard to more complex alkaloid skeletons, as illustrated in Figure 8 (THIQ's) and Figure 9 (THβC's).



Chirality denoted by asterisk.

Adapted from: Huber, I. M. P.; Seebach, D., *Helv. Chim. Acta* **1987,** *70,* 1944.

Figure 7 - Methods for the Asymmetric Synthesis of THIQ's and THβC's

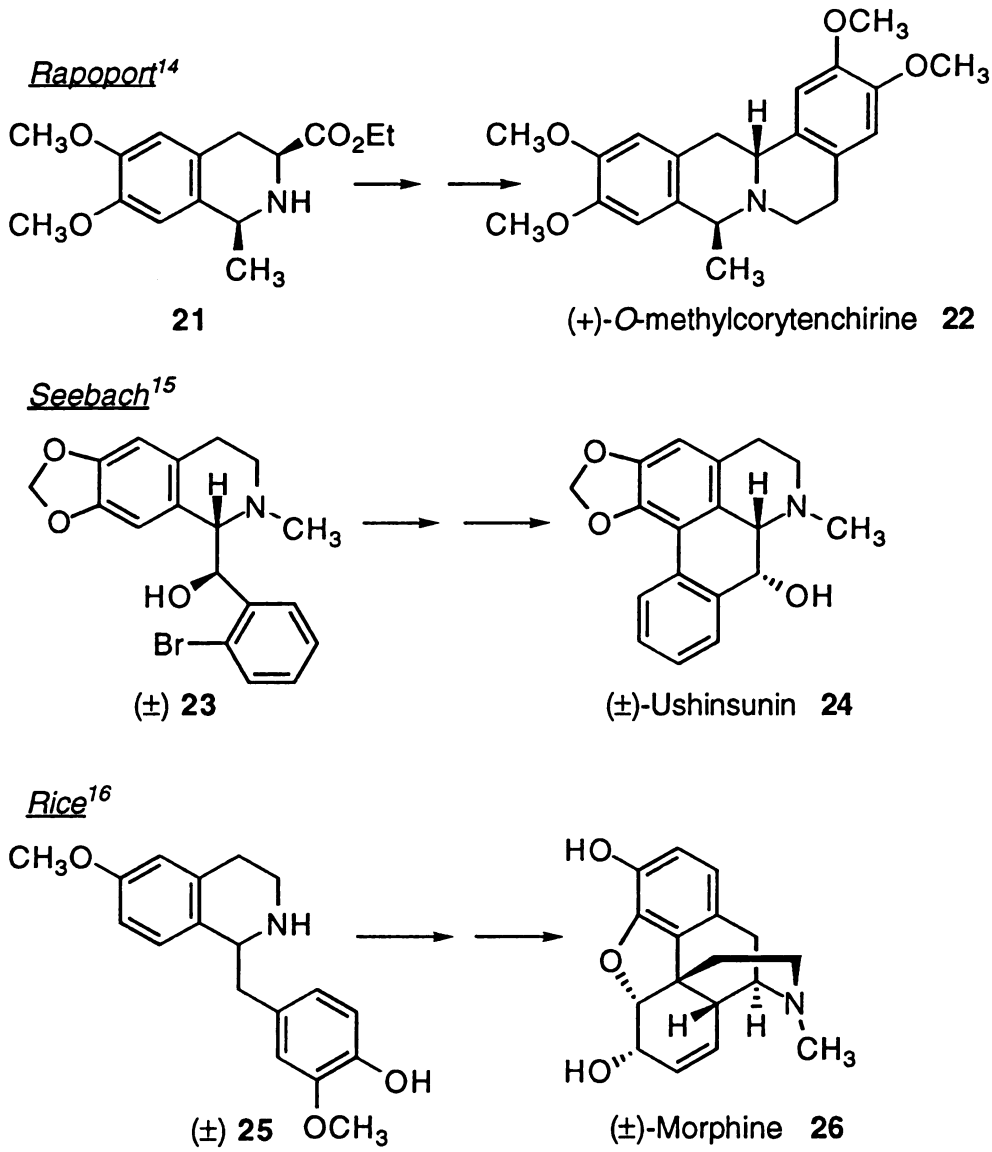
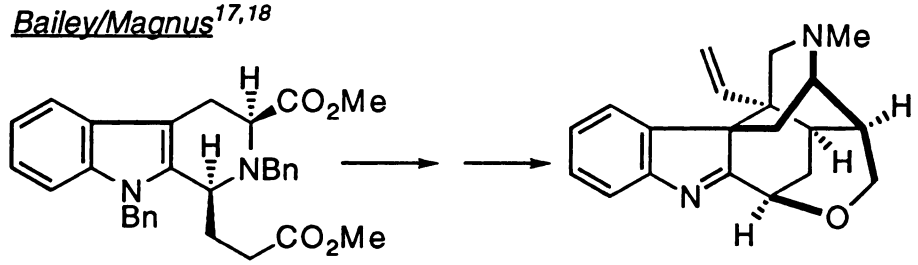


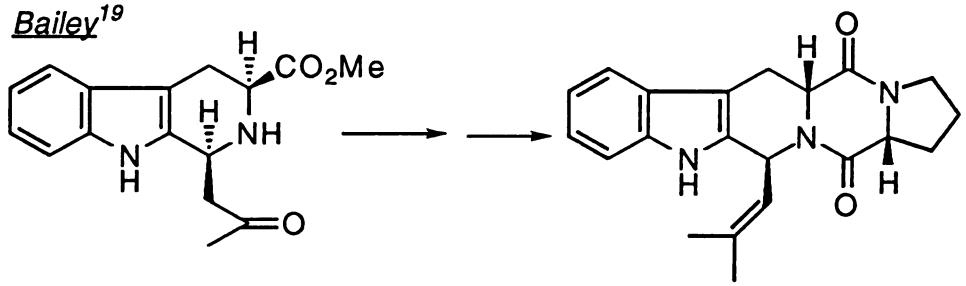
Figure 8 - Alkaloids Synthesized from THIQ Precursors

Bailey/Magnus[17,18]



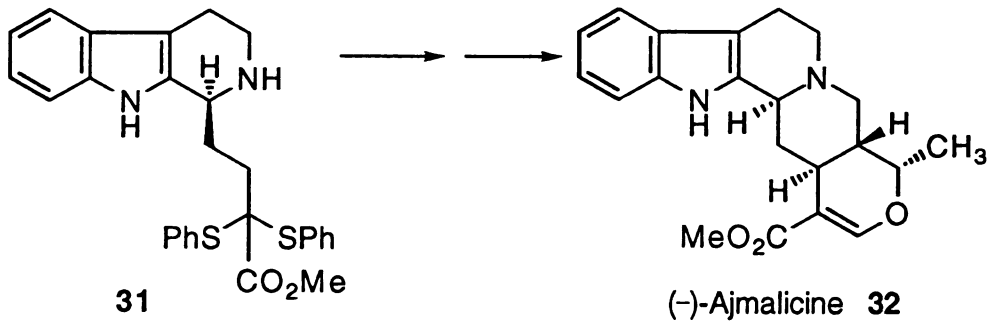
27 (−)-Koumine **28**

Bailey[19]



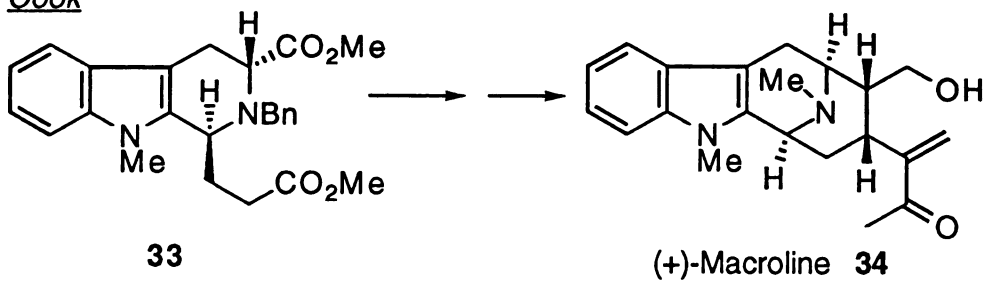
29 Demethoxy-fumitremorgin C **30**

Massiot[20]



31 (−)-Ajmalicine **32**

Cook[21]



33 (+)-Macroline **34**

Figure 9 - Alkaloids Synthesized from THβC Precursors

For over eighty years the Pictet-Spengler reaction,[22] illustrated in Figure 10, has played a prominent role in alkaloid synthesis. A reaction of the Mannich type, it involves the condensation of a β-arylamine and a reactive carbonyl compound. The formation of an intermediate Schiff base, followed by cyclization, yields a THIQ or tetrahydro-β-carboline (THβC). The cyclization is usually acid-catalyzed.

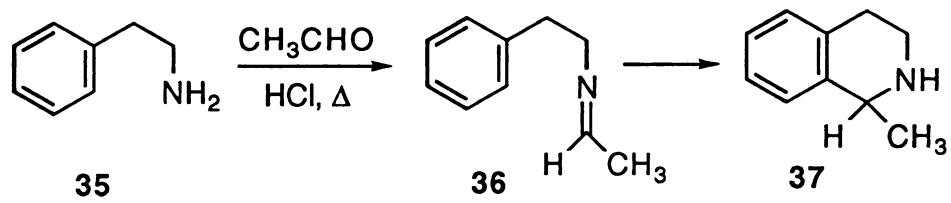


Figure 10 - Original Pictet-Spengler Reaction

When the β-arylamine component is an indole derivative, there are two conceivable pathways by which the cyclization could proceed (Figure 11).[22c,23b] Attack of the intermediate iminium ion may take place directly at the C-2 position of the indole to give carbonium ion **42** (path A), or at the C-3 position to give the spiroindolenine **41**, which then rearranges to give **42** (path B). While path B is generally believed to be the operative pathway, the reaction may proceed by direct attack when the iminium ion is very electrophilic.

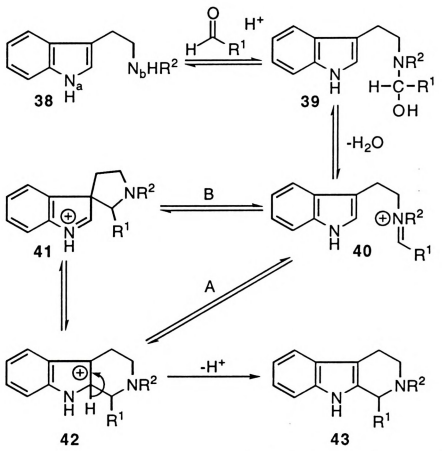


Figure 11 - Possible Pictet-Spengler Cyclization Pathways

If either the amine or carbonyl component is chiral, asymmetric induction is possible. Since aromatic amino acid derivatives provide a convenient and inexpensive source of chiral β-arylamines, their utility has been investigated with vigor.

The diastereomeric ratio obtained in the condensation of tryptophan derivatives with aldehydes (Figure 12) has been studied extensively, and has been found to be dependent upon the steric and electronic nature of the system as well as the reaction conditions.[22c,23] Early attempts to achieve stereocontrol typically gave mixtures of the cis and trans isomers with a few exceptions. As the factors governing the stereoselectivity of the reaction became better understood, the ratios improved, culminating with the attainment of 100% trans stereoselectivity in the reaction of N_b-diphenylmethyl substituted tryptophan esters with various aldehydes, yielding 1,3-disubstituted THβC's, as reported by Cook et al.[24]

Unfortunately, the stereochemistry of most naturally occurring THβC's is opposite that of the trans product obtained from the naturally occurring L-tryptophan. A general method for the specific production of 1,3-cis isomers has been elusive, although Massiot[25] has reported an instance of success in the condensation of L-tryptophanamide with 4-formyl-2,2-bis(phenylthio)butyrate. Similar reactions reported by Overman,[26] however, gave diastereomeric mixtures.

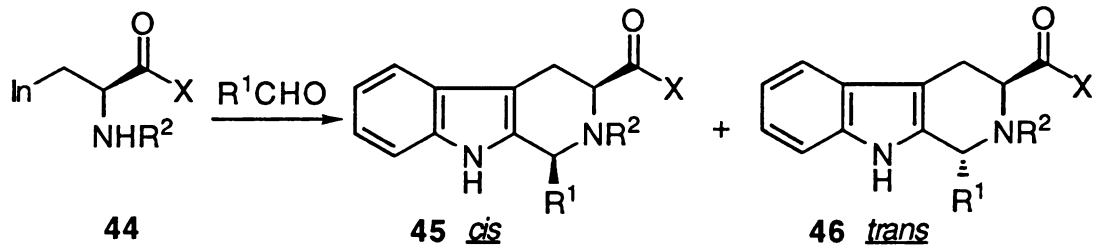


Figure 12 - Pictet-Spengler Reaction of Tryptophan Derivatives

Contrasting the many reports regarding tryptophan derivatives, only a handful of reports about the diastereomeric ratio obtained in the Pictet-Spengler condensation of phenylalanine derivatives have appeared. This may be due to the simple fact that the aromatic ring of phenylalanine does not readily undergo Pictet-Spengler cyclization, and therefore requires prior activation,[22b] via substitution with electron-donating groups, making tryptophan a more convenient choice for study. Asymmetric condensations involving L-DOPA [3-(3,4-dihydroxyphenyl)-L-alanine] or its alkylated derivatives reported by Brossi[27] and Yamada[6e,28] gave diastereomeric mixtures, with the 1,3-cis isomer predominating. Apparently, there have been no investigations of asymmetric Pictet-Spengler reactions involving *N*-substituted derivatives of the phenylalanine family. However, epimerization studies[6e,29] have shown that *N*-substituted THIQ's equilibrate to favor the 1,3-trans geometry to a much greater extent than do their unsubstituted counterparts, in accordance with the much studied asymmetric formation and epimerization of the THβC system.

In both systems racemization and epimerization of products is a concern. Racemization is believed to occur through tautomerization of the Schiff base intermediate **47** with the imine **48** before product formation (Figure 13).[23b,30]

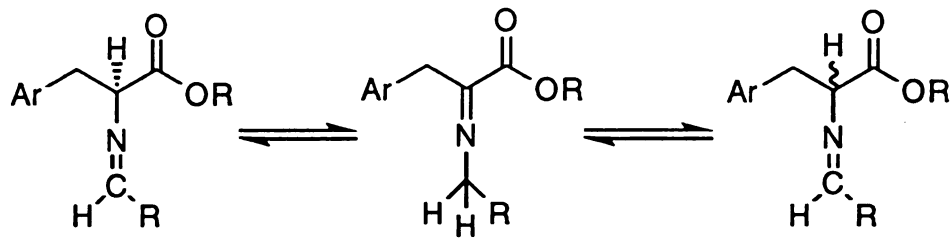


Figure 13 - Tautomerization of the Schiff Base

Epimerization may occur under a variety of conditions and has been advantageously employed in certain alkaloid syntheses.[6e,13,22c] Acid-catalyzed epimerization of THβC's occurs at C-1 and is believed to arise from expulsion of the protonated N_b nitrogen to form the stabilized cationic intermediate **52**, followed by re-formation of the ring to give epimerized product (Figure 14).[22c,23,31]

Similarly, properly substituted phenolic THIQ's have been observed to epimerize at C-1, presumably through the quinone methide intermediate **56** (Figure 15).[14,31] Acid-catalyzed epimerizations of either system generally require elevated temperatures, and the substitution pattern of the benzene ring largely determines the ease of the process.[23,31] Base catalyzed epimerizations may occur at C-3 in both systems through enolate formation, followed by re-protonation.[6e,30]

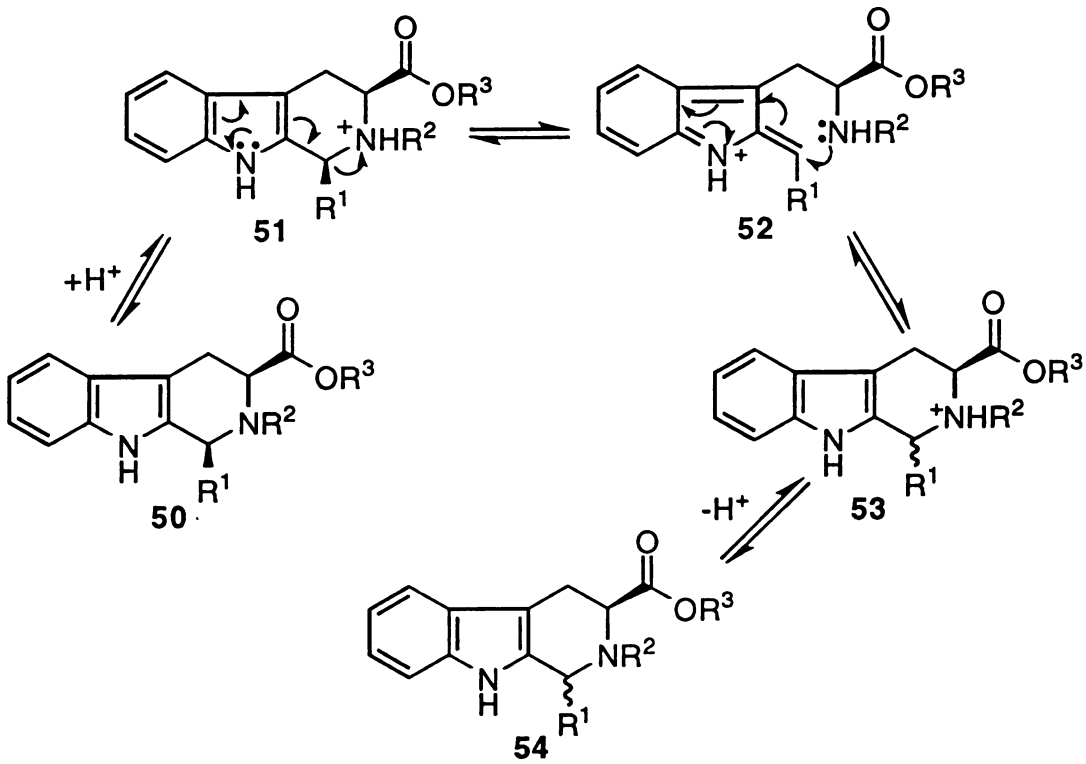


Figure 14 - Epimerization of THβC's

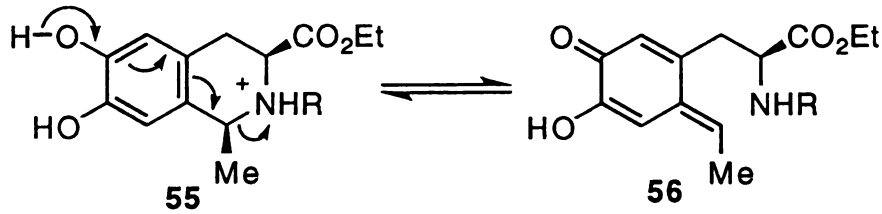


Figure 15 - Epimerization of THIQ's

Our tether mediated strategy may expand the usefulness of the asymmetric Pictet-Spengler reaction in several ways: 1) Conformational restriction should result in the exclusive formation of 1,3-cis disubstituted THIQ's and THβC's, which at C-1 leads to the stereochemistry usually found in nature, if the naturally occurring L-amino acid is employed. 2) By lowering the energy of activation, tethering the amine and carbonyl components may extend the range of practical substrates to include those displaying poor intermolecular reactivity. The enhanced reactivity is expected to arise from a favorable entropy effect, attributed to the intramolecular nature of the condensation, and a favorable enthalpy effect, attributed to the inductive effect of the tethering ester linkage, which should render the carbonyl, as well as the resulting Schiff base, more electrophilic. 3) The introduction of asymmetric quaternary centers at the crucial C-1 site may be possible. Though compounds containing such a structure are extremely rare in nature, such a technology could provide unnatural analogs having altered or enhanced physiological effects, that are presently unattainable. 4) Cleavage of the bridged lactone function of the cyclization product would provide reactive functionality at both the C-1 and C-3 appendages that may be exploited in the synthesis of more complex alkaloids. 5) The [3.3.1] bridged system should resist epimerization. If enolate formation at C-3 or acid-catalyzed elimination of the bridgehead nitrogen at C-1 were to occur, the remaining stereocenter would provide "memory" upon recyclization due to the same conformational restriction that directed the original ring closure.

This study aims to validate the feasibility of employing our tether mediated strategy to gain stereocontrolled entry into the THIQ and THβC ring systems, by the synthesis of the appropriate model compounds.

RESULTS AND DISCUSSION

Plan of the Study

Our temporary tethering strategy for stereocontrol in the Pictet-Spengler reaction is schematized below (Figure 16). The carboxyl group of the aromatic amino acid would function as a tethering site allowing the carbonyl component to be temporarily connected through an ester bond. The amino group would require protection during ester formation, and its deprotection would later allow the Pictet-Spengler condensation to commence. The stereocontrolled formation of δ-lactone **59**, which bears a new asymmetric center at C-1, would be followed by nucleophilic or reductive cleavage to give the di- or tri-substituted product **60**.

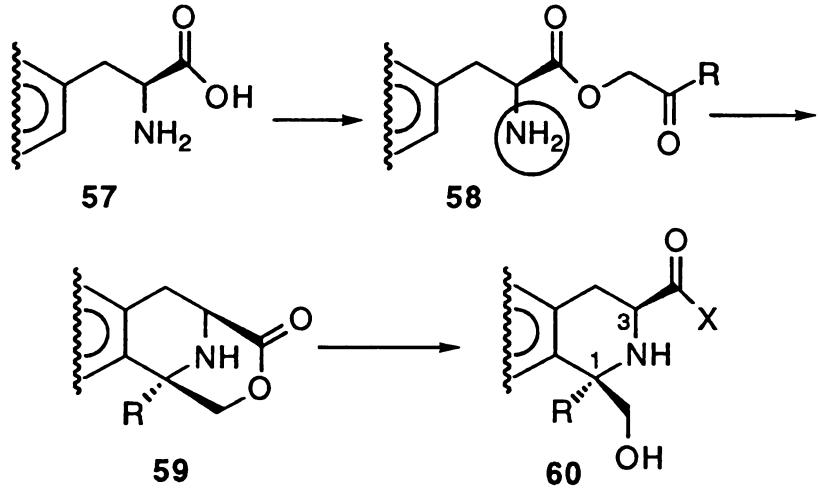


Figure 16 - General Strategy

We devised our model systems to facilitate the assessment of our scheme, and to cultivate methodological practicality. We explored the use of tryptophan, phenylalanine, and tyrosine as starting materials, but focused mainly on the use of tryptophan, due to the

demonstrated ability of the electron-rich indole nucleus to participate in Pictet-Spengler cyclization without prior modification. Numerous protective groups are available for the amino function.[32] We chose to feature two of the most versatile and widely used, the carbobenzoxy (Cbz) group and the *t*-butoxycarbonyl (Boc) group. We investigated both aldehyde and ketone carbonyl components, to demonstrate the generation of both tertiary and quaternary asymmetric centers, respectively, at the C-1 position.

Esterification of Protected Amino Acids: Formation of the Tethering Bond

For each of the model systems we investigated, the esterification of an *N*-protected amino acid with a functionalized alcohol played a key role. Since simple acid-catalyzed esterification gave poor results, we explored several other methods in pursuit of efficiency. The results are summarized in Table 1. We first examined the use of the coupling reagent 2-chloro-1-methylpyridinium iodide (MCPI), due to its reported effectiveness when acid sensitivity or steric bulkiness is a concern,[33] but the result was disappointing (entry a). Next, we tried the widely used 1,3-dicyclohexylcarbodiimide (DCC) as a coupling reagent, but found that the standard procedure[34] gave only moderate yields of the desired ester (entries b, d, e, h), along with a significant amount of a solid impurity, identified as the *N*-acylurea derivative of the protected amino acid (see product **63** in Figure 17).

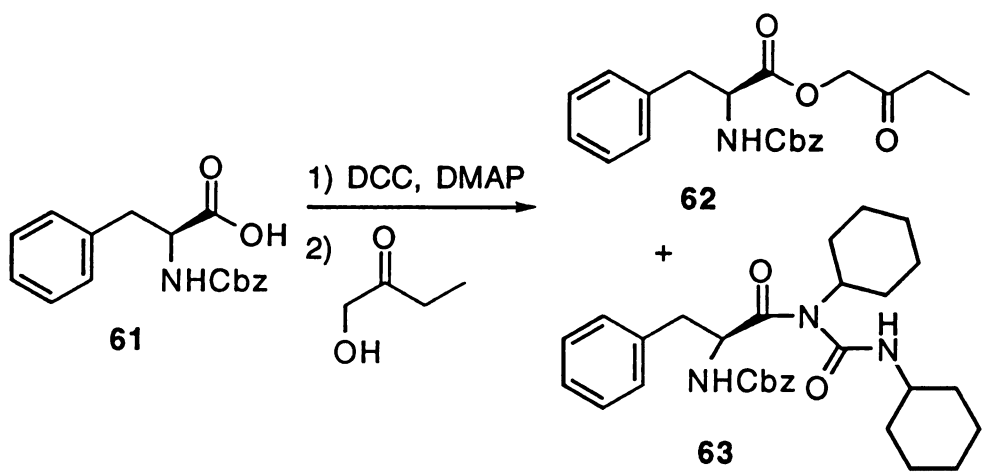
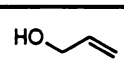
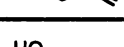
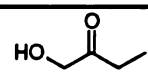
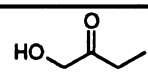
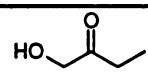
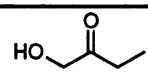
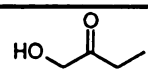
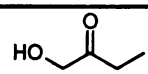
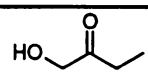
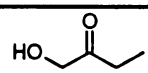
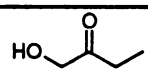


Figure 17 - Application of Traditional DCC Esterification

Table 1 - Esterification of Protected Amino Acids

entry	amino acid	alcohol	reagent(s)	solvent	yield	*ref.*
a	L-Trp-Z		MCPI/TEA	CH_2Cl_2	27	*33*
b	L-Trp-Z		DCC/DMAP	CH_2Cl_2	47	*34*
c	L-Trp-Z		TsCl	pyridine	87	*36*
d	L-Trp-Z		DCC/DMAP	CH_2Cl_2	26	*34*
e	L-Trp-Z		DCC/DMAP	CH_3CN	39	*34*
f	L-Trp-Z		TsCl	pyridine	85	*36*
g	D-Trp-Z		TsCl	pyridine	81	*36*
h	L-Phe-Z		DCC/DMAP	CH_2Cl_2	33	*34*
i	L-Phe-Z		DCC/TsOH	pyridine	86	*35*
j	L-Phe-Z		TsCl	pyridine	94	*36*
k	L-Tyr-Z		DCC/TsOH	pyridine	67	*35*
l	L-Trp-Boc		TsCl	pyridine	60	*36*

This side-product has been encountered often in DCC-mediated esterifications. Holmberg and Hansen[35] have reported that the addition of a catalytic amount of *para*-toluenesulfonic acid and the use of pyridine as the solvent greatly increases the yield of ester, while the *N*-acylurea formation is diminished. Their explanation of the role of the acid catalyst is illustrated in Figure 18. Employing this modification in the reaction of *N*-Cbz-L-phenylalanine with 1-hydroxy-2-butanone increased the yield of ester **62** to 86% (entry i), compared to 33% with the standard procedure (entry h). Simultaneously, we also investigated the classic ester preparation from mixed sulfonate anhydrides.[36] This method proved even more efficient than the acid-catalyzed DCC coupling procedure, providing the ester (entry j) **62** in 94% yield.

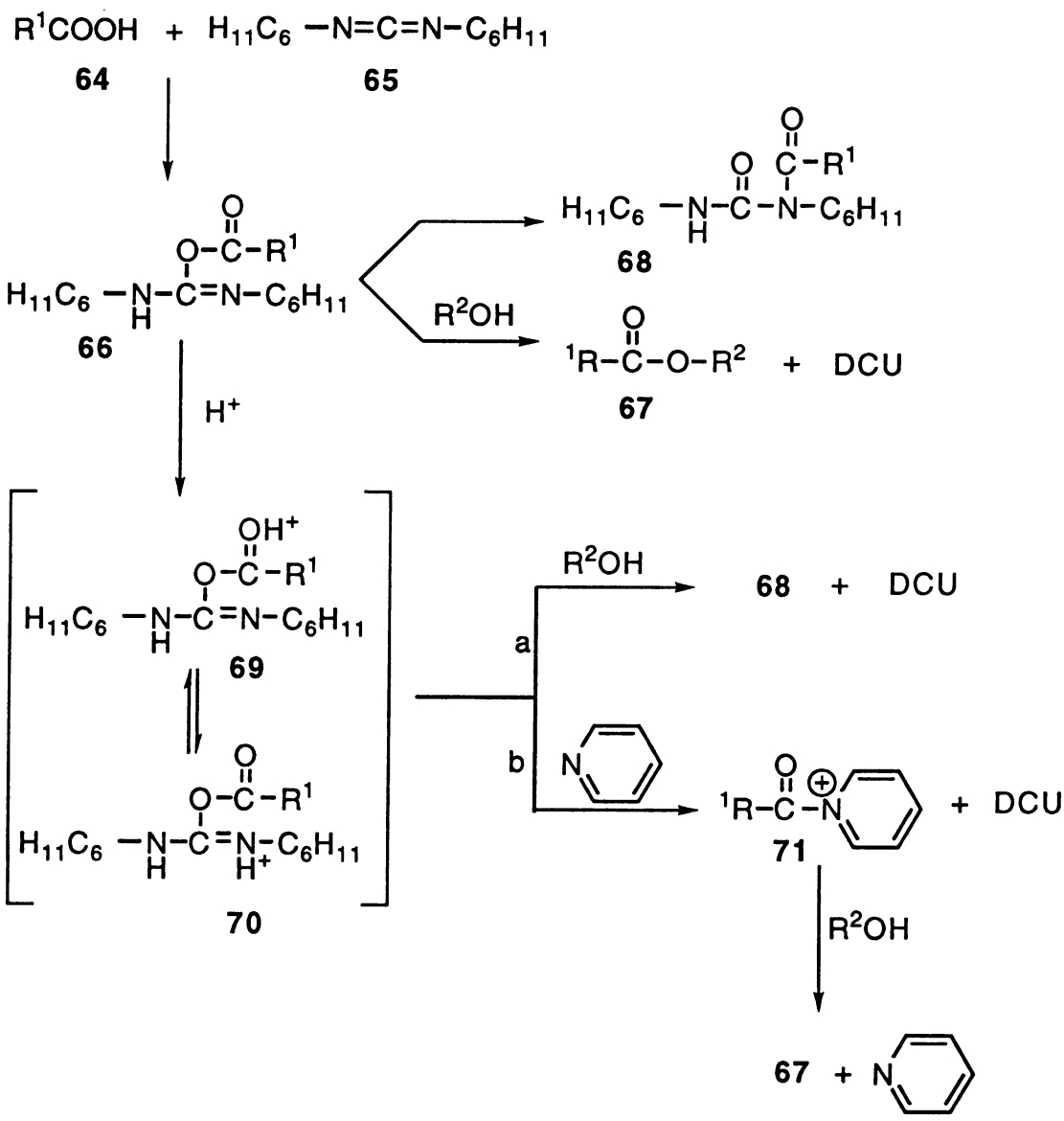


Figure 18 - Role of Acid Catalyst in DCC Esterification

Synthesis of a THβC Bearing an Asymmetric Quaternary Center at C-1

We felt that the tethered ketone precursor necessary for this synthesis could be prepared by direct coupling of the protected amino acid with an α-hydroxyketone, and were pleased to find that 1-hydroxy-2-butanone is commercially available. *N*-Cbz-L-tryptophan was prepared from the amino acid by a modified Schotten-Baumann procedure,[37] or obtained directly from a commercial supplier. The coupling of these components was best achieved by reaction of the alcohol with the mixed *para*-toluenesulfonate anhydride of the protected amino acid, as described above, to give acyl ester **73** in 85% yield (Figure 19).

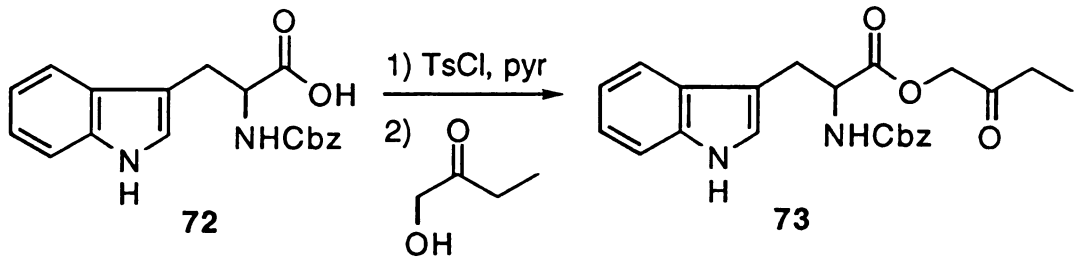


Figure 19 - Preparation of Acyl Ester 73

Expecting that amino deprotection would occur without complication by way of standard hydrogenolysis, an ethanolic solution of **73** was stirred at room temperature under an atmosphere of hydrogen, in the presence of 10% palladium on carbon (Figure 20). Carbobenzoxy cleavage initiated the spontaneous intramolecular condensation of the amino group with the tethered ketone of **74** (not isolated) to give the cyclic Schiff base **75**, but in a disappointing 42% yield. The major side product was tryptophan (**76**), apparently generated by the hydrogenolysis of the acyl ester. The possible side reaction intermediate **72** was not isolated. While benzyl, allyl and vinyl esters are known to be susceptible to catalytic hydrogenolysis, we were surprised to find that the acyl group weakened the carbon-oxygen bond sufficiently to promote cleavage. Only one other such example was

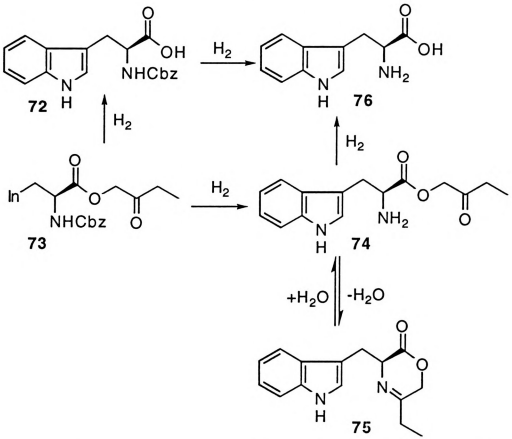


Figure 20 - Hydrogenolysis of Tethered Ketone Precursor 73

found in the literature, and in this case the acyl group was substituted with a 2-benzofuran ring, making it more electron-deficient than normal.[38] Similarly, the enhanced reactivity of **73** may be due to the electron-withdrawing effect of the *N*-Cbz group on the ester function. Performing the reaction at 0 °C suppressed the undesired acyl ester cleavage, raising the yield of the cyclic imine **75** to 92%.

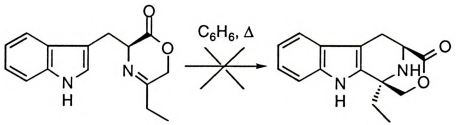
The reaction of aliphatic ketones with amines to form imines is reputed to require elevated temperatures and the removal of water from the reaction mixture to shift the equilibrium in favor of the product, and acid catalysis is often employed.[39] The formation of imine **75** without these aids can be attributed to intramolecularity and perhaps the electron-withdrawing effect of the ester substitution on the α-carbon. It is likely that hydrogenolysis of the acyl ester bond of **73** does not occur once the imine is formed, since the carbon-nitrogen double bond is less polar than the carbonyl bond. This prompted us to speculate that the removal of water from the reaction mixture would prevent equilibration of the Schiff base with the tethered amino ketone **74**, mitigating the reductive cleavage of the acyl ester. However, the addition of water (11 equivalents) to the reaction reduced the yield only slightly to 81%, compared to a range of 85 - 92% for the anhydrous reaction. Also, the use of molecular sieves (3 Å) hampered the hydrogenation, resulting in incomplete deprotection over a comparable reaction time. Given the excellent results obtained without the sieves, and the modest effect of added water, their use was deemed unworthy of further investigation.

Changing the catalyst to palladium hydroxide (moist), known to be highly effective for the hydrogenolysis of benzyl groups,[40] gave a modest 78% yield of the imine. Catalytic transfer hydrogenolysis, with ammonium formate[41] as the transfer agent, gave the imine in only 69% yield. Other known methods of deprotection[32] were investigated but found comparatively ineffective. These include treatment with trimethylsilyl iodide, methanesulfonic acid/anisole, HBr/acetic acid and BF_3 etherate.

A molecular ion peak at m/z 256 in the mass spectrum of the isolated product provided evidence that the condensation did occur. The basis for the identification of the product as the Schiff base **75**, as opposed to the isomeric Pictet-Spengler cyclization product, is the existence of a carbon-nitrogen double bond stretch at 1696 cm^{-1} in the IR spectrum, as well the proton NMR. The coupling relationships in the aliphatic region of the two possible products were expected to be similar, and the absolute chemical shifts were difficult to anticipate. However, the presence of five aromatic hydrogens in the Schiff base, as opposed to four in the Pictet-Spengler product, was easily determined by integration ratios.

The Pictet-Spengler reaction traditionally has been carried out in one step from the amine and carbonyl components in protic solvents, in the presence of an acid catalyst.[22] However, Cook *et al.* reported[42] that in the neutral, aprotic medium of refluxing benzene, tryptophan methyl ester derivatives and aldehydes reacted to give higher yields of THβC's than in aqueous, acidic media. We found this encouraging, due to concerns that cleavage of the tethering bond might occur under traditional reaction conditions.

With this is mind, Schiff base **75** was refluxed in dry benzene. Unfortunately, analysis of the reaction by thin layer chromatography (TLC) revealed that only starting material was present after 12 hours.



75 **77a**

Figure 21 - Attempted Cyclization in Aprotic Medium

The failure of **75** to cyclize under Cook's conditions may be due to ring strain in the bridged, tetracyclic framework of **77a**, or in the spiroindolenine intermediate that precedes it, raising the energy of the transition state relative to non-tethered carbonyls. Alternatively, the imine may be less reactive than those studied by Cook, resulting in no cyclization. Compared to imines derived from aldehydes, those derived from ketones are more sterically crowded, and are less electrophilic due to the electron-releasing property of the additional alkyl group. In the case of imine **75** this is probably not true, since the additional alkyl group is substituted with an electron-withdrawing ester function. Cook *et al.* have demonstrated[42] that modest structural changes can affect the electrophilicity of the imine, and hence the outcome of the reaction (Figure 22). When refluxed in benzene in the presence of benzaldehyde, tryptamine yielded only imine **80**, while the less basic amine, tryptophan methyl ester, yielded the Pictet-Spengler product **82**. Likewise, salicylaldehyde reacted with tryptamine under the same conditions to yield only imine **84** (eq. 2a), while acetylsalicylaldehyde gave the rearranged Pictet-Spengler product **86** (eq. 2b).

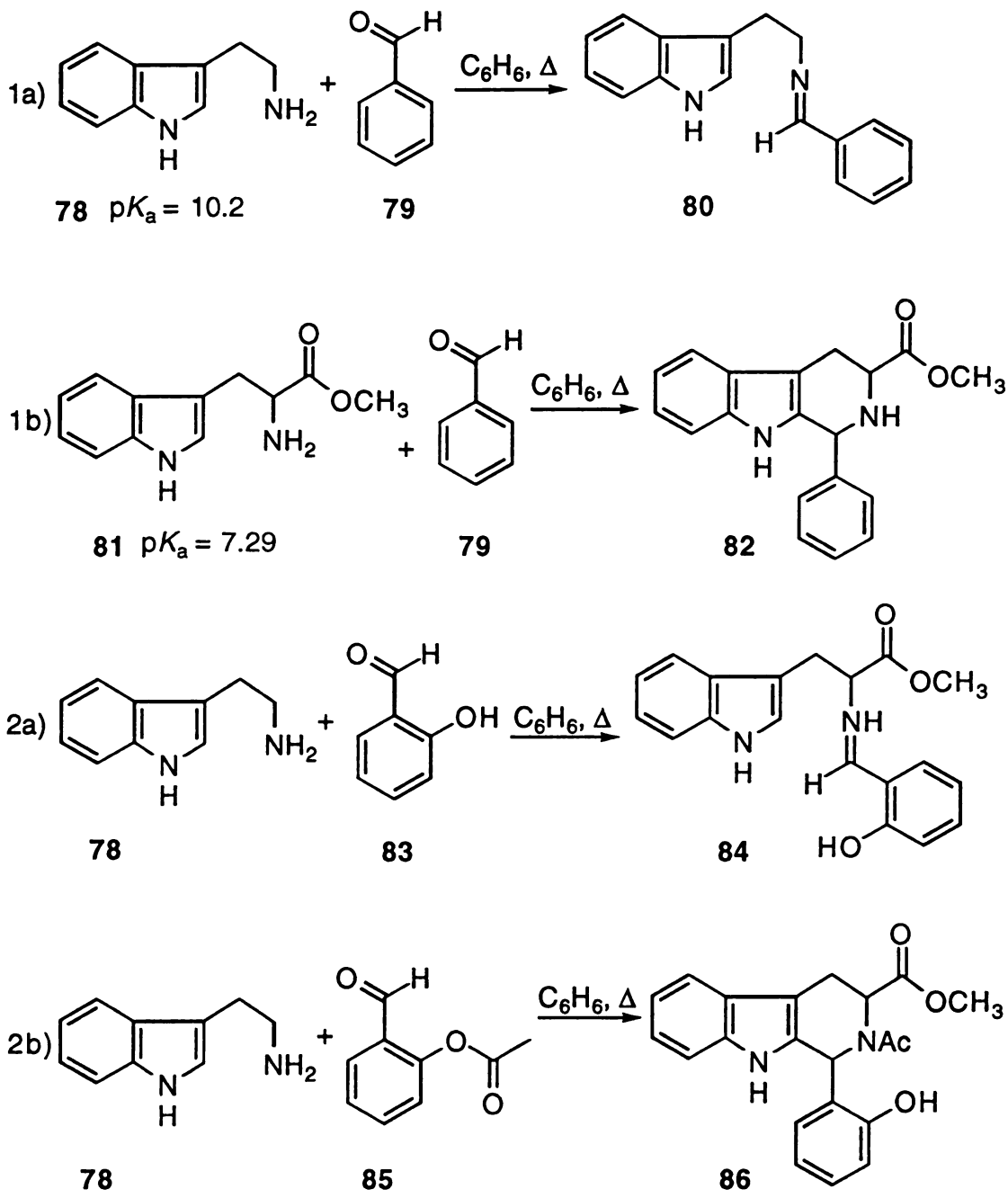


Figure 22 - Effect of Imine Electrophilicity in the Pictet-Spengler Reaction

The addition of an acid catalyst was next examined in an effort to cyclize Schiff base **75**. To the previously refluxed solution of **75** in benzene, an anhydrous solution of *p*-toluenesulfonic acid (0.11 equivalents in benzene) was added, and refluxing was resumed. TLC revealed the slow but steady emergence of a single new product spot. The conversion was complete after 11 days. Purification by flash chromatography yielded a white crystalline solid.

To evaluate the enantiomeric purity of the product, we planned to use ^{1}H NMR chiral lanthanide shift reagents.[43] First, it was necessary to obtain a normal spectrum of the product. Because chiral lanthanide shift reagents are effective only in non-complexing NMR solvents, deuterated chloroform was employed, even though the product was only sparingly soluble in chloroform at room temperature. Heating was required to accomplish dissolution. Surprisingly, the resulting spectrum indicated the presence of two distinct species, in a ratio of 3:1 (Figure 23).

We speculated that perhaps heating the sample in deuterated chloroform resulted in the formation of the second species, and therefore decided to obtain a spectrum in deuterated acetone, a solvent in which dissolution is easily achieved at room temperature. The resulting spectrum indicated the presence of only a single species, supporting our suspicion (Figure 24).

We were not convinced, however, since TLC of the sample prepared in deuterated chloroform for NMR still revealed only a single product spot. To determine if a solvent effect was responsible for the disparity of the two spectra obtained, the solvent was removed *in vacuo* from the deuterated chloroform sample, and the residue redissolved deuterated acetone. The result was dramatic; only a single magnetic resonance signature was present, identical to the spectrum obtained previously by direct dissolution in deuterated acetone.

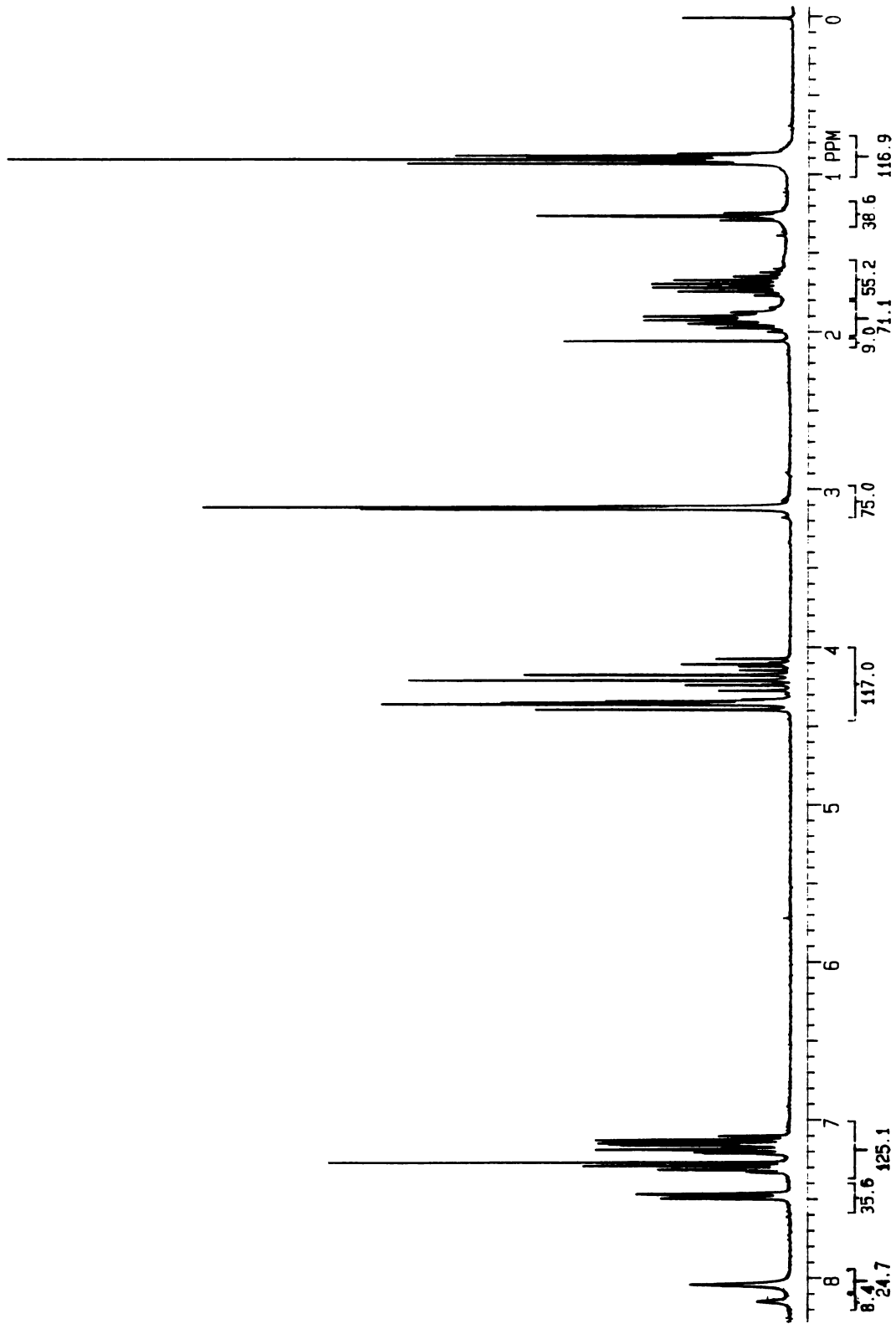


Figure 23 - ^{1}H NMR Spectrum in $CDCl_3$ of Reaction Product

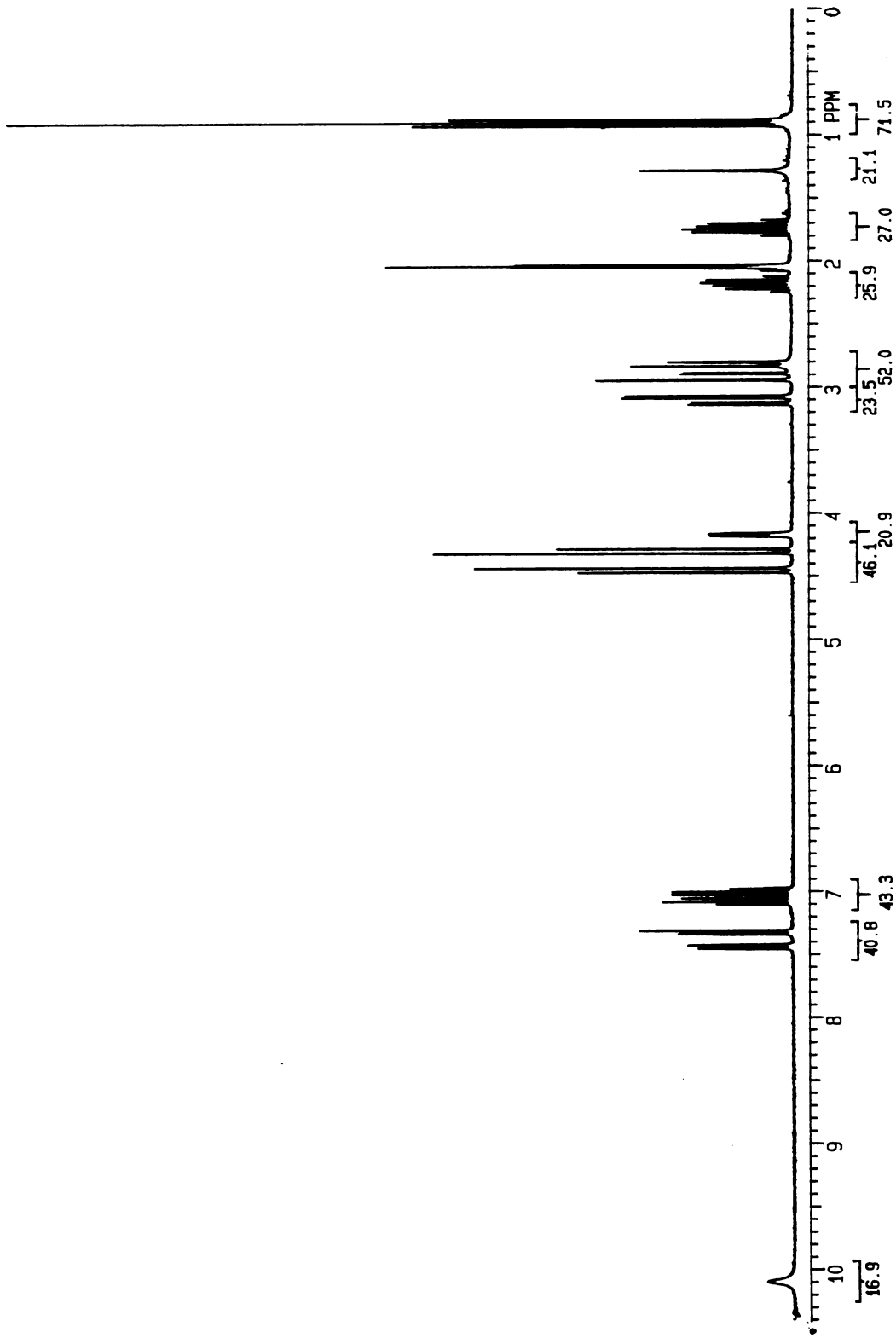


Figure 24 - ^{1}H NMR Spectrum in Acetone-d_6 of Reaction Product

Proton NMR spectra were then obtained in deuterated chloroform in the presence of the chiral shift reagent Resolve-Al™ [europium tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate), Sievers's Reagent]. No additional signals were observed, which would have indicated the presence of a third or fourth species -- the enantiomeric partners of the original species. However, the reagent did effect the separation of several overlapping signals, making the spectrum easier to interpret.

The mass spectrum gave a parent ion at m/e 256, identical with that of the Schiff base precursor, suggesting only a rearrangement of atoms had occurred, as would be true of the Pictet-Spengler product **77a**. In addition, the base peak at m/e 197 indicates the presence of 1-ethylcarbolinium cation, that could be generated from **77a** by cleavage of the bridged lactone and aromatization. All aspects of the ^{1}H NMR spectrum obtained in deuterated acetone were also consistent with **77a**, key indicators being the loss of one aromatic proton, relative to the Schiff base, and a new high field signal consistent with an *N*-H proton. The spectra obtained in deuterated chloroform in the presence of Resolve-Al™ allowed us to evaluate the identity of both components. The signals corresponding to both the major and minor components were consistent with **77a**, and we postulated that the product consists of a 3:1 ratio of enantiomers **77a** and **77b** (Figure 25). The apparent enantiomeric differentiation observed when the spectrum was taken in deuterated chloroform was reasoned to arise from unusually strong solute-solute hydrogen bonding interactions, resulting in an equilibrating series of dimeric complexes. Since these interactions are diminished in the strongly complexing deuterated acetone, enantiomeric differentiation is not observed. However, our initial literature search failed to reveal a precedent for this behavior.

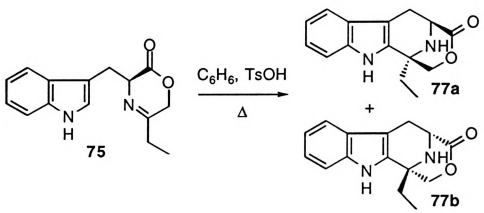


Figure 25 - Cyclization with Racemization

While we were disappointed that the product was partially racemized, we were excited at the prospect of uncovering a new NMR phenomenon. To test our hypothesis, it was necessary to achieve our original goal of synthesizing **77a** in enantiomerically pure form.

Racemization, via tautomerization of the Schiff base (Figure 13), is expected to be hastened by heating and acid catalysis.[23,31] A method that avoids both would be ideal. Woodward's push-pull approach[44] to the spiroindolenine **88**, employed en route to strychnine (Figure 26, eq. 1), fits these criteria. Electrophilic attack by tosyl chloride on the imine nitrogen and deprotonation of the indolic *N*-H bond by pyridine resulted in cyclization to give sulfonamide **88**, a more stable product than the analogous indolenium salt that failed to form when **87** was treated with acid. However, Woodward notes that this reaction may be a special case, since the carbon-nitrogen double bond of the product is conjugated with the veratryl group. This suspicion was supported by the observation[45] that spiroindolenine **90** was not formed when 2-methylbenzylidene tryptamine (**89**) was subjected to these conditions (Figure 26, eq. 2). However, the benzylidene derivative of tryptamine reacted under these conditions to give the THβC **91** (Figure 26, eq. 3).

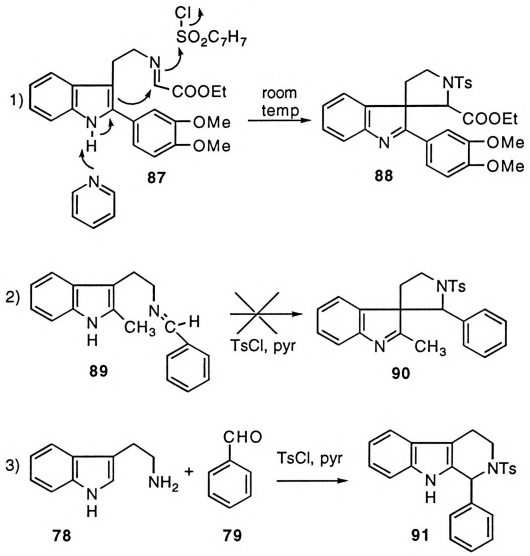


Figure 26 - Woodward's Push-Pull Approach

Unfortunately, no useful results were attained by treating imine **75** under these conditions. Substituting a stronger base, triethylamine in methylene chloride, gave no reaction at room temperature (Figure 27).

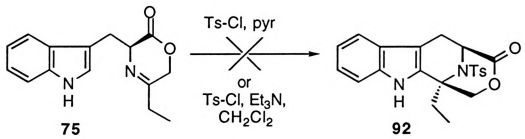


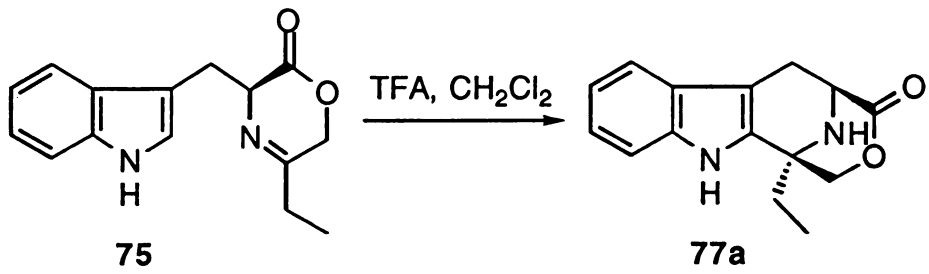
Figure 27 - Treatment of Schiff Base 75 with TsCl

Further literature review revealed an alternative set of Pictet-Spengler reaction conditions -- methylene chloride/trifluoroacetic acid -- in which THβC's are formed at room temperature.[25,46] In addition, these reaction conditions are reported to effectively mitigate the racemization problem.[23,47]

This was our experience also. Schiff base **75** was treated according to the method of Ottenheijm.[46] As when treated in refluxing benzene/TsOH, a single product spot was evident by TLC, and a white crystalline product was isolated. However, the ^{1}H NMR spectrum obtained in deuterated chloroform indicated the presence of only one species, consistent with **77a**. The addition of Resolve Al™ gave no indication that the antipode of **77a** was present. The spectrum in deuterated acetone was identical to that obtained earlier. The product was also found to be optically active, ruling out the possibility that complete racemization had occurred.

In order to confirm that the ^{1}H NMR of the original sample was indeed exhibiting enantiomeric differentiation, we repeated the synthetic sequence beginning with D-tryptophan. The end product displayed a ^{1}H NMR spectrum identical to that derived from L-tryptophan, and an inverted optical rotation. A spectrum was then obtained for a 4:1 mixture of the D- and L-derived products in deuterated chloroform. Again, the presence of

two distinct species was indicated, establishing at once two important facts; the synthesis of **77a** had been achieved enantiospecifically (Figure 28), and enantiomeric differentiation is observed in the ^1H NMR for non-racemic mixtures of the enantiomers.



75 **77a**

Figure 28 - Stereospecific Cyclization

We soon learned that this unusual NMR phenomenon had been previously observed, and while rare, had been thoroughly studied and well documented.[48] Known as self-induced nonequivalence, it is rationalized by considering the average environment of each enantiomer generated through binary solute-solute associations (Figure 29). For example, when the L-enantiomer is the predominant isomer, the D-form is associated mainly as the heterochiral dimer (equation 2), and the L-form mainly as the homochiral dimer (equation 3). Since each enantiomer exists in a different average environment, different NMR signals are observed for each. If the association constants are weak, the enantiomers exist mainly in their unassociated states and give identical NMR signals, accounting for the rarity of self-induced nonequivalence. A strongly complexing solvent will compete for binding sites, diminishing the association constant and resulting in the appearance of only one NMR signal. This is what we observed when changing the NMR solvent from deuterated chloroform to deuterated acetone. In the case of a racemic sample, the average environment of each enantiomer is identical, resulting in one NMR signal, although the chemical shifts may deviate from those of an optically pure sample.

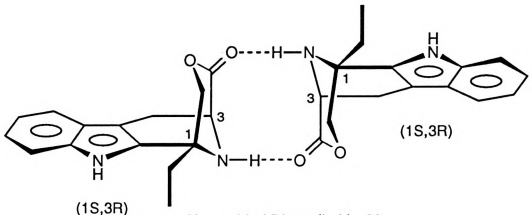
1) $D + D \rightleftharpoons D \cdot D$

2) $D + L \rightleftharpoons D \cdot L$

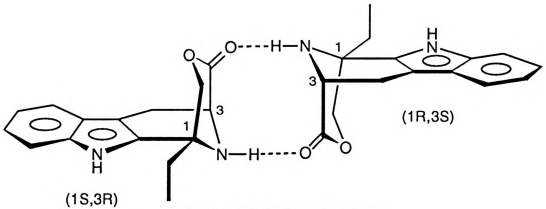
3) $L + L \rightleftharpoons L \cdot L$

Figure 29 - Binary Solute-Solute Associations of Enantiomers

A common trait of the small group of compounds reported to display self-induced nonequivalence is the ability to form particularly strong hydrogen bonding interactions, and in most cases a cyclic dimeric complex has been invoked to explain the tendency to associate.[48b] We propose the bidentate, hydrogen bonded dimers **93** and **94**, modeled in Figure 30, to account for the NMR behavior of **77**.



Homochiral Dimer (L• L) **93**



Heterochiral Dimer (L• D) **94**

Figure 30 - Proposed Dimeric Structures

The large number of protective groups available for the amino function provide many options for variation of our strategy. The prospect of performing the deprotection and Pictet-Spengler reaction in one step prompted us to investigate the use of the *t*-butoxycarbonyl (Boc) protecting group, since a commonly used combination of reagents for the cleavage of the Boc group is methylene chloride/trifluoroacetic acid, the same reagents that we found to be effective in the stereospecific cyclization of **75** to **77a.**

N_α-(*t*-butoxycarbonyl)-L-tryptophan **95** was prepared from the amino acid and di-*t*-butyl dicarbonate, according to the method of Keller *et al.*,[49] or purchased directly from a commercial supplier. The coupling of the Boc-protected amino acid and 1-hydroxy-2-butanone was achieved by the reaction of the alcohol with the mixed para-toluenesulfonate anhydride of the protected amino acid, providing acyl ester **96** in a 60% yield (Figure 31).

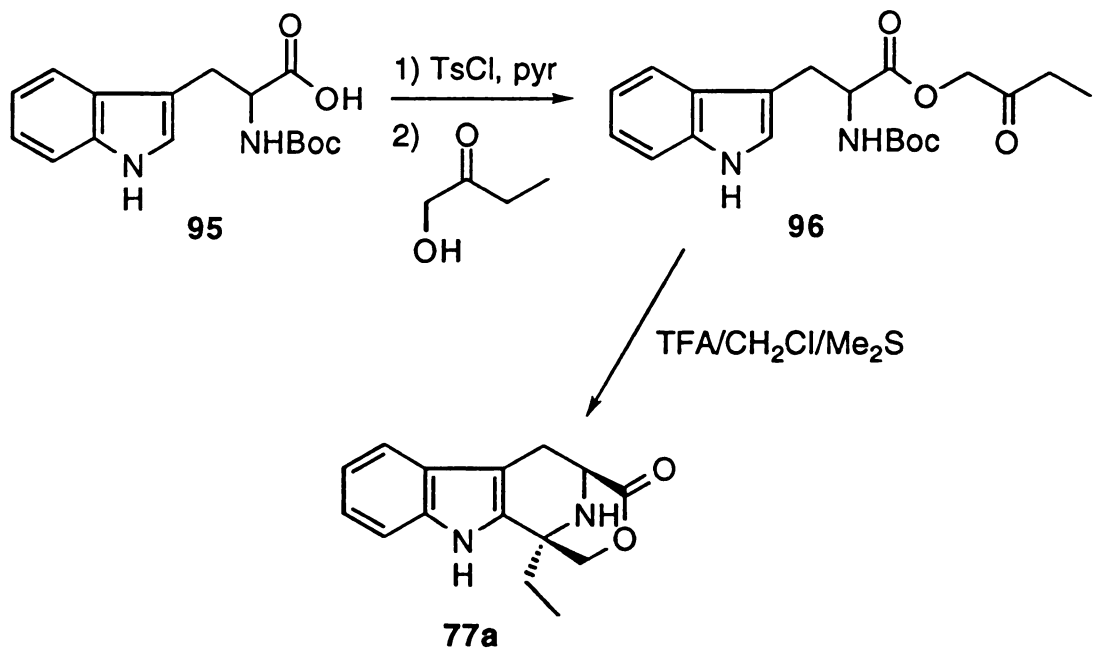


Figure 31 - One Step Deprotection/Cyclization

Our major concern in employing the Boc protecting group was that the indole ring may be alkylated by the cations generated during deprotection, or undergo general oxidative degradation, two types of side reactions often encountered in peptide synthesis.[50] Cation

scavengers, usually thiols or thioethers, are commonly used to combat these problems. Treatment of the *N*-Boc protected tethered ketone **96** with a 2% solution of trifluoroacetic acid in methylene chloride, in the presence of one equivalent of dimethyl sulfide, gave the desired Pictet-Spengler product **77a** in a yield of 60%.

Having successfully achieved the crucial stereospecific synthesis of bridged lactone **77a** from both Boc- and Cbz-protected tryptophan, we turned our attention to the cleavage of the tethering bond. We chose to effect this cleavage through ammonolysis, since the generation of an amide functionality at C-3 sets the stage for the eventual removal of the carboxyl carbon, if desired, through Yamada's procedure[51] for the reductive decyanization of α-amino nitriles (Figure 32).

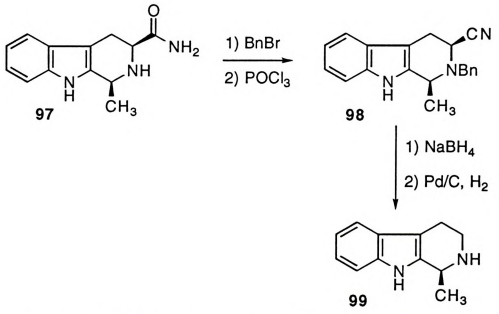
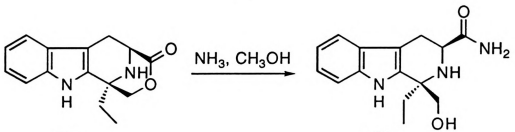


Figure 32 - Yamada's Reductive Decyanization Sequence



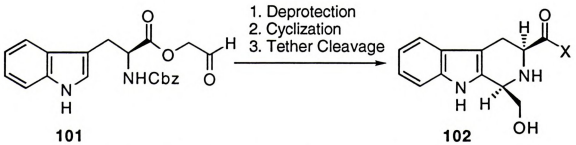
77a 100

Figure 33 - Tether Cleavage via Ammonolysis

To this end, treatment of lactone **77a** with a cold, saturated solution of methanolic ammonia proceeded smoothly, giving a quantitative yield of the hydroxy amide **100** (Figure 33).

Synthesis of a THβC Bearing an Asymmetric Tertiary Center at C-1

This synthesis requires the preparation of tethered aldehyde derivatives. We chose to investigate the behavior of formylmethylester **101**, which upon cyclization and cleavage would give a THβC bearing a hydroxymethyl substitution at the newly created asymmetric center (Figure 34), analogous to the proposed fragment **5** in our retrosynthetic analysis of Et 729 (see Figures 1 and 3). The direct coupling approach to aldehyde **101** was ruled out due to the instability of glycolaldehyde[52] and the expense of the corresponding acetals. Our indirect approach utilizes allyl alcohol as an inexpensive, stable synthetic equivalent of glycolaldehyde.



101 102

Figure 34 - Anticipated Behavior of Tethered Aldehyde 101

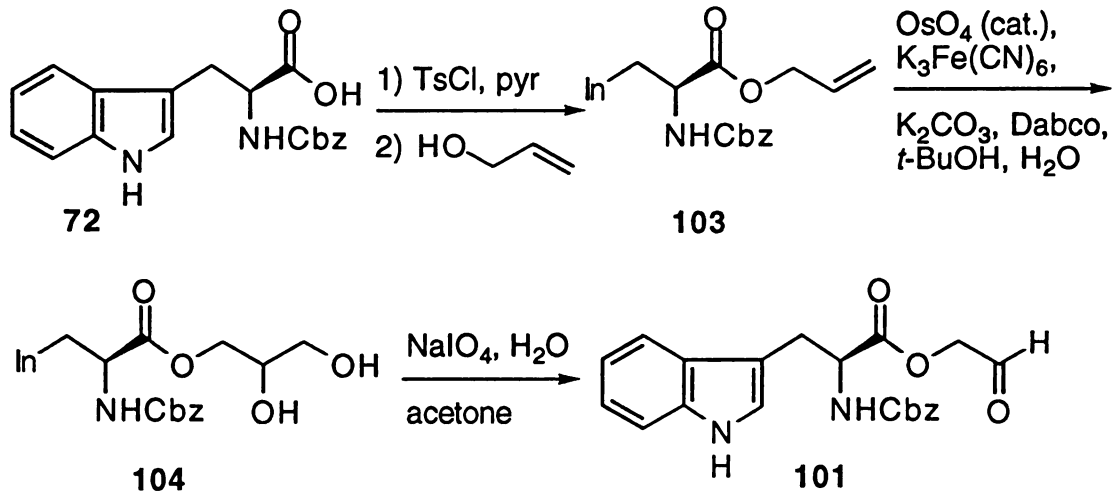


Figure 35 - Preparation of Tethered Aldehyde Precursor 101

Allyl ester **103** was formed in 87% yield by treating the mixed sulfonate anhydride of the protected amino acid with ally alcohol. The next task was to effect the oxidative cleavage of the olefin, while avoiding oxidation of the indole moiety. Ozonolysis was ruled out since ozone has been reported to oxidize the 2,3-bond of indole derivatives.[53] Likewise, periodate ion is known to oxidize the indole ring,[54] making the application of one-step methods[55] that employ a catalytic amount of glycolating agent in the presence of periodate seem unattractive. However, periodate has been used to selectively cleave pre-formed 1,2-diols of compounds containing an indole function without oxidizing the indole ring.[12,56] Conversion of the olefin to the diol **104** was accomplished in a yield of 66%, using a catalytic amount of osmium tetroxide, with potassium ferricyanide/potassium carbonate as the cooxidant, a practice introduced by Minato *et al.*[57] and popularized by Sharpless,[58] as a feature of his asymmetric dihydroxylation procedure. Tertiary amines are known to accelerate the catalysis. Therefore, 1,4-diazabicyclo[2.2.2]octane (Dabco™) was added to the reaction mixture.[57] The dihydroxylation of the olefin results in the creation of an additional chiral center. Proton NMR analysis revealed the preponderance of one of the diastereomers in the purified product mixture. Since the new stereocenter is removed in the next step, no attempt was made to separate the diastereomers. Treatment of

this isomeric mixture of diols with sodium metaperiodate, according to the method of van Tamelen,[56a] gave the desired aldehyde **101** in a yield of 79%, along with 11% of recovered starting material. Though the reaction seemed to progress smoothly, it stubbornly resisted going to completion, even with the addition of more periodate.

With the tethered aldehyde **101** in hand, we were confident that deprotection and cyclization could be easily accomplished using the methodology developed for the preparation of **77**. Contrary to our expectations, this objective was achieved only after extensive study.

Treatment of **101** with hydrogen in the presence of 10% palladium on carbon, in ethanol at 0 °C -- reaction conditions which successfully led to deprotection and imine formation with tethered ketone **73** -- failed to remove the blocking group. Performing the reaction at room temperature again led to the recovery of starting material, as did changing the solvent to benzene. Likewise, changing the catalyst to palladium on calcium carbonate also failed to effect hydrogenolysis. When the hydrogenation was attempted in the presence of hydrochloric acid in methanol, a pink oil was obtained, an outcome associated with the degradation of indole-containing molecules.[50a]

These surprising results caused us to re-evaluate the structural assignment of **101**. An area of concern in the proton NMR was that the resonance assigned to the aldehyde proton at δ 9.35 ppm appeared as a sharp singlet, instead of the expected apparent triplet or doublet of doublets resulting from coupling of the vicinal methylene group, which typically ranges from 1 to 3 Hz.[59] A spectrum was thus obtained on a high field (500 MHz) instrument, but also failed to reveal any splitting of this resonance. If the coupling in this case is unusually small, the resonance should still experience broadening which can be determined by a decoupling experiment. When the vicinal methylene (δ 4.6 ppm) was irradiated, the line width at half height of the resonance at δ 9.35 ppm was reduced to 2.35 Hz from the original width of 2.67 Hz, supporting our structural assignment.

Some insight into the inability to effect this seemingly routine deprotection was provided by Freifelder,[60] who observed that hydrogenolysis may be retarded by the presence of catalyst poisoning impurities in the substrate. Freifelder suggests pretreating the unreactive substrate with Raney nickel (10 - 15% by weight) and/or activated carbon to remove the impurities. Therefore, **101** was pretreated with Raney nickel and activated charcoal and subjected to hydrogenation in the presence of 10% palladium on carbon in ethanol at 0 °C (Figure 36). After 4 hours TLC showed that most of the starting material was still present. The reaction was then allowed to proceed at room temperature, and after an additional 13 hours the reaction was halted, as only a small amount of starting material was evident by TLC. Unfortunately, the main reaction product isolated was tryptophan (60% yield), resulting from cleavage of the acyl ester linkage as well as the protecting group. None of the expected cyclic imine **107** was isolated; however, we were able to isolate a small amount of the hydrogenated product **108** (10% yield). These results raised serious concern that standard hydrogenolysis of **101** to yield **107** was not a viable option, since undesired hydrogenolysis of the acyl ester linkage of tethered aldehyde **101** appeared to be much more facile than in the previously discussed case of tethered ketone **73**, and because the cyclic imine was susceptible to hydrogenation of the carbon nitrogen double bond, with the possibility that any imine which escaped hydrogenation decomposed upon workup and isolation.

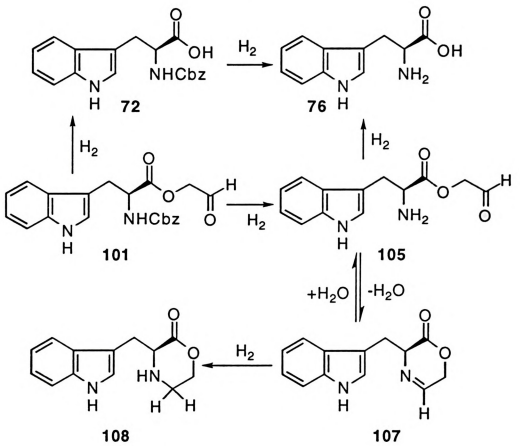


Figure 36 - Catalytic Hydrogenation of Pretreated 101

Thus, an alternative route was devised to avoid these pitfalls (Figure 37). By converting the aldehyde **103** to its corresponding acetal, the linkage should become stable to hydrogenolysis. In addition, we suspected that the catalyst poisoning problem would be eliminated with removal of the aldehyde function, since the only difference between the successfully deprotected ketone **73** and problematic aldehyde **101** is the nature of the tethered carbonyl. The relative difficulty experienced in purifying **101** bolstered this suspicion. Deprotected acetal could then be subjected to Pictet-Spengler cyclization. The successful use of acetals as aldehyde equivalents in this reaction is well documented.[61]

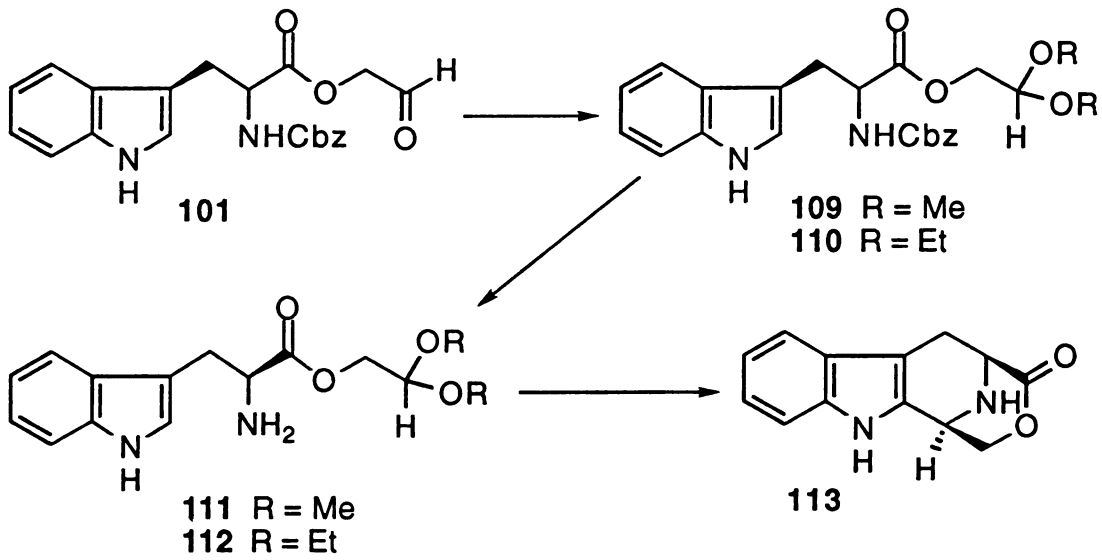


Figure 37 - Alternative Route via Acetal

Aldehyde **101** was converted to its methyl acetal **109** by treatment with trimethyl orthoformate and catalytic *p*-toluenesulfonic acid in methanol in a yield of 76%. The hydrogenolysis of the carbobenzoxy protecting group then proceeded smoothly to give **111** (H_2, Pd/C, EtOH, 97% yield).

The deprotected acetal was then treated with trifluoroacetic acid (1.3 eq) in methylene chloride at room temperature, but only starting material was recovered after 3 days. Increasing the amount of trifluoroacetic acid (13.7 eq) also gave no reaction (Figure 38).

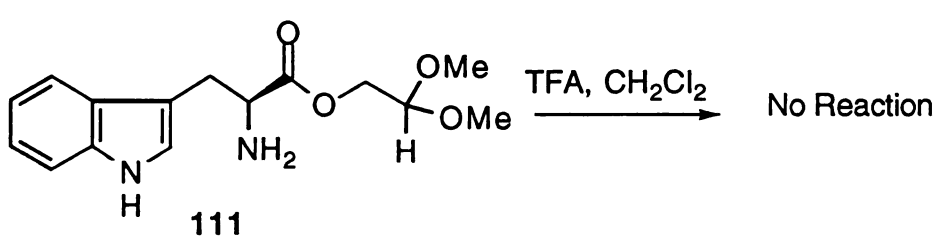
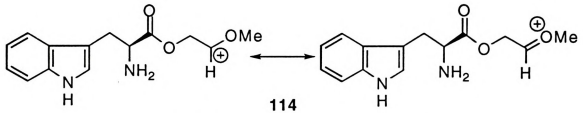


Figure 38 - Treatment of Methyl Acetal 111 with TFA

This was surprising, since similar reactions have proven successful.[61] In addition, since the formation of acetals from simple alcohols is known to be a reversible process with the

equilibrium constant favoring the aldehyde,[62] we felt that switching the nucleophile from water to an intramolecular amino group on a flexible tether would create an even more favorable equilibrium for the *in situ* formation of the imine. This led us to speculate that perhaps the activation energy for the formation of the oxonium ion intermediate **114** was prohibitive in the trifluoroacetic acid/methylene chloride medium. Furthermore, because the same oxonium intermediate was involved in the formation of the acetal, it must be stabilized sufficiently under the conditions of formation.



114

Figure 39 - Oxonium Ion Intermediate

The ability of methanol to solvate cations was reasoned to account for this divergent behavior. Thus, we decided to attempt cyclization of **111** under conditions similar to those used in the acetal formation -- refluxing methanol and catalytic *p*-toluenesulfonic acid (0.026 eq). A reaction ensued, but the only product recovered was tryptophan methyl ester. When the reaction was run at room temperature with trifluoroacetic acid (2.0 eq), mainly starting material was recovered along with a small amount of tryptophan methyl ester. Reasoning that a non-nucleophilic but polar solvent would stabilize the oxonium ion but not result in trans-esterification, we switched the solvent to acetonitrile. After 30 hours no reaction was observed, so 5 Å molecular sieves were added to trap any methanol that might reform the acetal, but this had no effect. Heating the mixture to reflux also failed to produce a reaction. Valls *et al.*[61a] successfully promoted the conversion of **115** to **116** using *p*-toluenesulfonic acid in benzene at room temperature (Figure 40), but these conditions returned only starting material in our case.

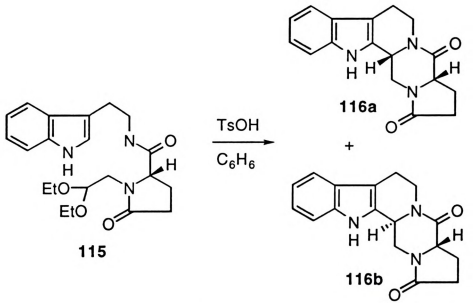


Figure 40 - Intramolecular Cyclization by Valls *et al.*

The *in situ* hydrolysis of diethyl acetals to aldehydes was employed by van Maarseveen *et al.*[63] to effect Pictet-Spengler cyclization, leading to the Eudistomin framework (Figure 41). The application of these conditions to **111** was also unsuccessful. These workers pointed out that the diethyl acetals are much easier to hydrolyze than the corresponding dimethyl acetals. Therefore, we synthesized the corresponding diethyl acetal **112** in the same manner as described for methyl acetal **111**. Again, however, treatment with chloroform/trifluoroacetic acid/water mixture was unsuccessful, yielding a complex mixture of products. When treated with trichloroacetic acid (1.0 eq) in methylene chloride the diethyl acetal **112** behaved no differently than the methyl acetal **111**, giving no reaction even after 2 weeks at room temperature.

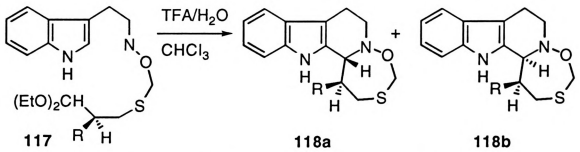


Figure 41 - van Maarseveen's *In Situ* Hydrolysis Method

The failure to achieve the Pictet-Spengler condensation of acetals **111** and **112** under conditions known to be effective suggests that a structural feature unique to these species is responsible for this anomalous behavior. The electron-withdrawing ability of the ester function results in a partial positive charge on the carbon α to the acetal, destabilizing alkoxonium ion **114** relative to those generated from ordinary acetals, which could account for the lack of reactivity. The field of carbohydrate chemistry provides numerous examples of acetal reactivity being reduced by the inductive effect of nearby heteroatoms.[64] Silverman and Ding[65] have shown that even when the electron-withdrawing group is three bonds removed from an acetal center, the rate of hydrolysis is significantly reduced. Most pertinent to our study was their finding that the relative rate of hydrolysis for γ-lactone acetal **120** was only 1.3×10^{-4} that of the saturated analog **119** (Figure 42).

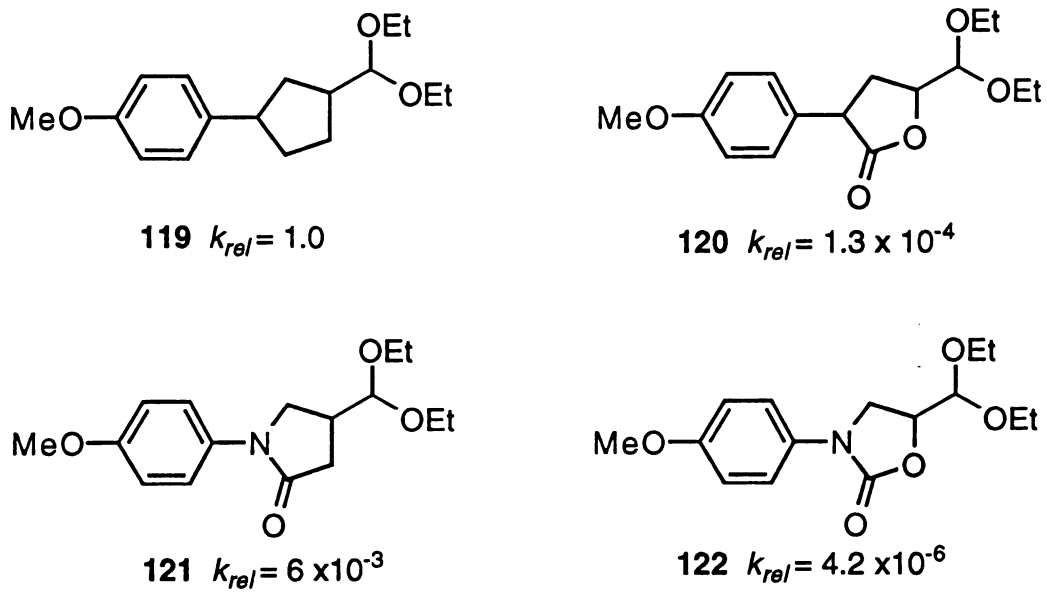
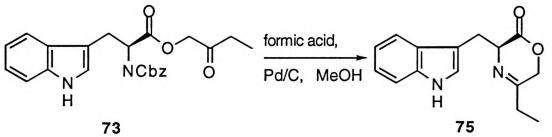


Figure 42 - Effect of Electron-Withdrawing Groups on Acetal Hydrolysis

Finding the acetal route to be unworkable, we focused our attention once again on finding a suitable means for the deprotection of aldehyde **101**, and chose to investigate catalytic transfer hydrogenation[66] for this purpose. Compared with reduction systems using a catalyst and molecular hydrogen, catalytic transfer hydrogenation offers an additional variable -- the hydrogen donor -- which may affect the rate and specificity of the reduction, both of which were problematic when molecular hydrogen was employed in the attempted deprotection of **101**.

Early indications regarding the use of formic acid as the hydrogen donor[67] were encouraging. The *N*-Cbz protected amino aldehyde **101** was treated with 4.4% formic acid in methanol in the presence of 10% Pd/C at room temperature. Thin layer chromatography revealed that all starting material was consumed after only five minutes, with the appearance of a single product spot. However, this product could not be isolated. Filtration gave a clear, colorless solution, but removal of the volatile materials *in vacuo* gave a yellow resinous material. TLC analysis revealed that the original product was no longer present, with the sample clinging to the baseline. For comparison, tethered ketone

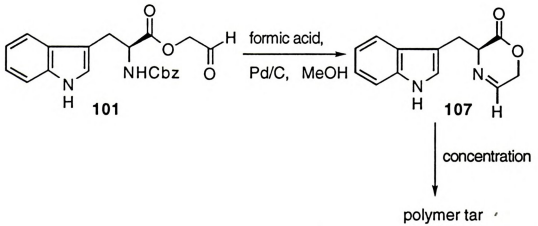
73 was treated under these conditions, giving imine **75** in good yield, the same product obtained previously with molecular hydrogen.



73 **75**

Figure 43 - Hydrogenolysis of 73 with Formic Acid as Hydrogen Donor

We suspect that hydrogenolysis of the carbobenzoxy group of **101** led to the rapid formation of imine **107**, in line with the behavior of tethered ketone **73** upon amino deprotection (Figure 44). Decomposition of the Schiff base is believed to have subsequently occurred upon isolation, giving the yellow tar. A review of the literature revealed that the stability of imines varies greatly with their structure.[39] Those formed from primary aldehydes are prone to polymerization through an aldol-like process, and are extremely difficult to isolate.



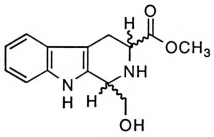
101 **107**

Figure 44 - Possible Outcome of Formic Acid Hydrogenolysis of 101

To circumvent the polymerization problem, the two-step reaction was attempted without isolation of the Schiff base intermediate, even though this meant sacrificing the

preferred cyclization solvent (methylene chloride), for one with dramatically different properties (methanol). During the deprotection stage the reaction vessel was immersed in an ice bath to further reduce polymerization. After the starting material had been consumed the trifluoroacetic acid catalyst (11.4 eq) was added and the reaction allowed to continue at room temperature.

The product isolated from this reaction exhibits spectral properties that are inconsistent with the expected tetracyclic bridged lactone **113**. An additional signal is present in the ^{13}C NMR spectrum. The proton NMR spectrum (DMSO) displays a three-hydrogen singlet (δ 3.72 ppm) and a one-hydrogen triplet (δ 5.00 ppm), which are clearly incompatible with structure **113**. The one-hydrogen triplet coalesces over time with residual water to give a broad singlet along with the concomitant simplification of one-hydrogen multiplets centered at δ 3.65 and δ 3.75, to the less complex doublet of doublets splitting pattern, suggesting it is an exchangeable hydrogen adjacent to an AB methylene group. This data along with a parent ion at m/z 260 in the mass spectrum strongly suggests that methanolysis of the tethering bond has occurred to give **123** (Figure 45). The first order coupling relationships, as determined by a ^{1}H COSY NMR experiment, are consistent with this structure.



123

Figure 45 - Methanolysis Product

While the crude yields of this product were quite good (66 - 98%), the purified yield after chromatography on silica gel was a disappointing 29%, lower than expected based on an examination of the crude proton NMR spectra. This raises the possibility that **123** may be susceptible to decomposition on silica gel.

The timing of the tethering bond cleavage is crucial to the stereochemical outcome of the reaction. Only if the cleavage occurs after the Pictet-Spengler cyclization will conformational restriction be maintained, and the product will be the *cis*-1,3-disubstituted THβC (Figure 46). If cleavage occurs before cyclization this element of stereocontrol is lost and either diastereomer can form, with a mixture being expected, based on the numerous reports of the reaction of tryptophan esters with aldehydes.[22c,23]

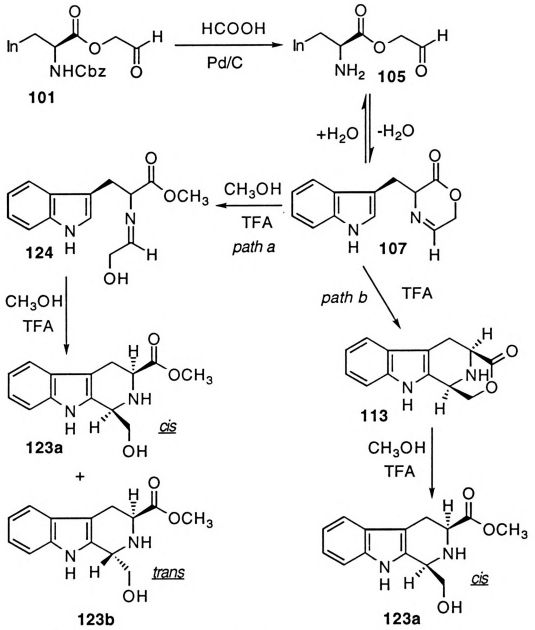


Figure 46 - Possible Pathways for the Formation of 123

Only one product was isolated by column chromatography. Precedent indicated that the stereochemistry of this product could be determined by nuclear Overhauser effect (NOE) difference spectroscopy. This technique was employed by Nicolaou[68] to determine similar stereochemical relationships in the structures of compounds **125** and **126**. Irradiation of the C-4 methyl signal of compound **125** caused a 30 % NOE enhancement of the C-10 proton signal, confirming their syn relationship. Likewise, an NOE enhancement of 14% was invoked to assign the syn relationship between H_a and H_b of compound **126**, which was later confirmed by the X-ray crystal structure of a derivative of compound **126**. NOE techniques were also used by Cook[69] to determine the stereochemistry of the six-membered nitrogen heterocycles **127**, **128**, and **129**.

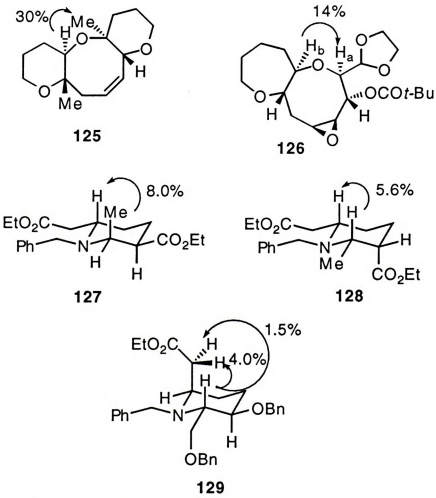


Figure 47 - Pertinent NOE Enhancement Precedents

Application of the NOE experiment to product **123** revealed that it was the *cis* isomer (Figure 48). Irradiation of C-1 proton resulted in an 8.7% enhancement of the C-3 proton signal, which was revealed as a clean doublet of doublets in the difference spectrum, after subtraction of the overlapping methyl ester singlet in the normal spectrum. Likewise, irradiation of the C-3 proton resulted in a 1.9% enhancement of the C-1 proton signal, and no enhancement of the C-1 methylene signals. Irradiation of the C-1 methylene signals gave no enhancement of the C-3 proton signal.

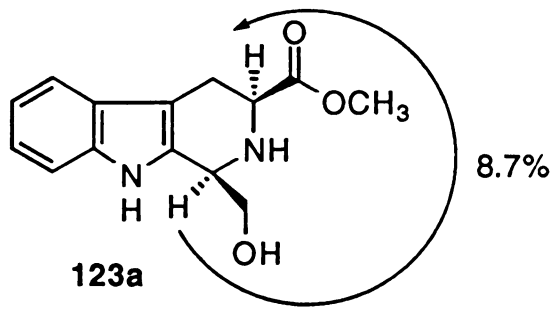
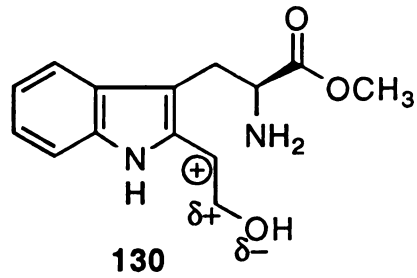


Figure 48 - NOE for 123

The isolation of only the *cis* diastereomer agrees with expectations for a scenario in which methanolysis occurs after formation of the tetracyclic bridged lactone **113**. The relief of ring strain in the bridged lactone framework is believed to be the driving force for the methanolysis. It is possible, however, that methanolysis occurred before the Pictet-Spengler reaction and still gave stereospecific formation of the cis isomer for reasons peculiar to this substrate, or that small amounts of the trans isomer were formed but not isolated. There is also the question of whether **123** is susceptible to epimerization at C-1 under the reaction conditions employed (methanol, formic acid, Pd-C, trifluoroacetic acid, room temperature, 4 days). As described in the introduction, the mechanism of epimerization has been determined to involve protonation of the N_b nitrogen, followed by cleavage of the C-1/N_b bond to give a resonance stabilized cationic intermediate, followed by reformation of this bond. Such epimerizations have been carried out on 1,3-disubstituted THβC's in refluxing methanolic hydrogen chloride.[23] We are unaware of

any reported epimerizations that have been carried out at room temperature in methanol. Also, it is likely that **123** is more resistant to epimerization than C-1 alkyl substituted THβC's, because the cationic intermediate species **130** is destabilized by the inductive effect of the hydroxyl function.



130

Figure 49 - Destabilizing Effect of Hydroxyl on Epimerization Intermediate

Separate from the epimerization concern, is the question of racemization (Figure 13). The solubility of **123a** in only polar, complexing solvents precluded the use of NMR chiral shift reagents for the determination of enantiomeric purity. However, a strong optical rotation ($[\alpha]_D = -118°$, MeOH, c = 0.11g/100 mL) indicates the maintenance of at least a degree of enantiomeric integrity.

Studies Employing Tyrosine as the β-arylethylamine Component

The formation of THIQ's through the Pictet-Spengler reaction usually requires an electron-rich benzene ring, or more specifically the presence of an electron-donating group *para* to the point of ring closure.[22] Despite this, we decided to test L-tyrosine as the β-arylethylamine component in an attempt to demonstrate our temporary tethering strategy could also be applied to the synthesis of the THIQ ring system. We wondered if the small activating effect of the hydroxyl substituent of L-tyrosine, although *meta* to the point of ring closure, in combination with the increased electrophilicity of the tethered imine intermediate, would be sufficient to prompt the reaction. The alternative, ring activation through placement of an electron-donating group in the 3-position of L-tyrosine, would require a multi-step sequence. Therefore, the risk was deemed worth taking.

The coupling of *N*-Cbz-L-tyrosine and 1-hydroxy-2-butanone was accomplished through a variation of Holmberg and Hansen's procedure[35] using DCC in pyridine in the presence of catalytic *p*-toluenesulfonic acid. Excess alcohol used was increased to 4.4 equivalents to help reduce the formation of by-product **133**, which results through the competitive esterification by the phenolic hydroxyl of tyrosine. The tethered ketone **132** was obtained in 67% yield, along with a 15% yield of **133**.

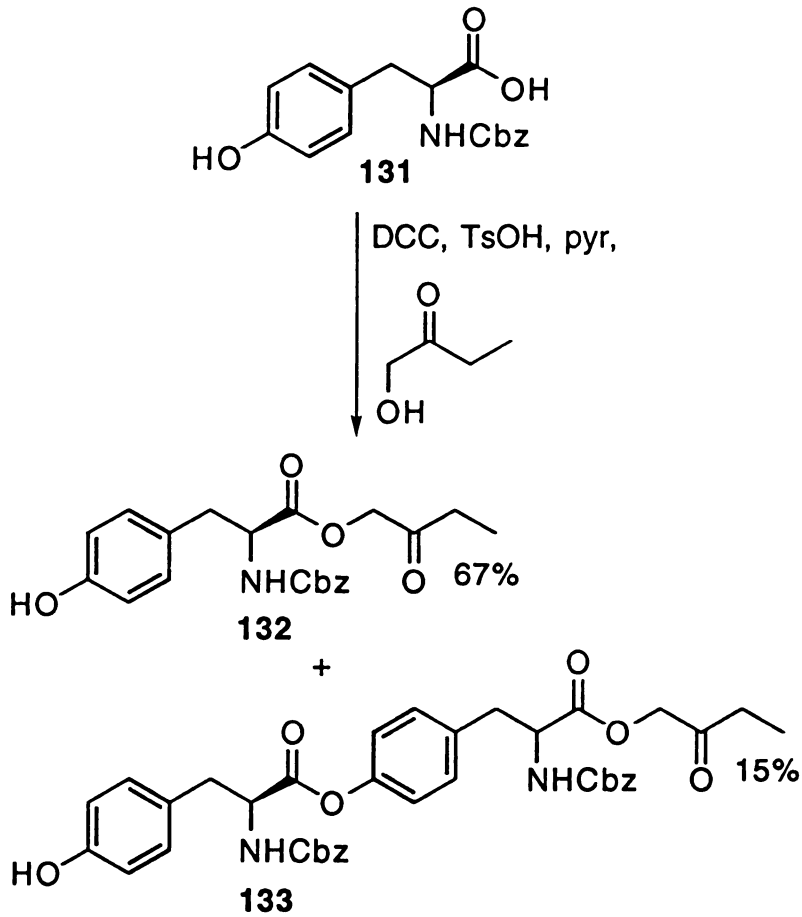


Figure 50 - Esterification of *N*-Cbz-L-Tyrosine

The cyclic Schiff base **136** was obtained in only 16% yield on hydrogenation of **132** (Figure 51). The reaction was complicated by competing hydrogenolysis of the acyl ester bond, as well as hydrogenation of the carbon-nitrogen double bond, which made

purification difficult. Unfortunately, treatment of **134** with trifluoroacetic acid in methylene chloride failed to induce Pictet-Spengler cyclization.

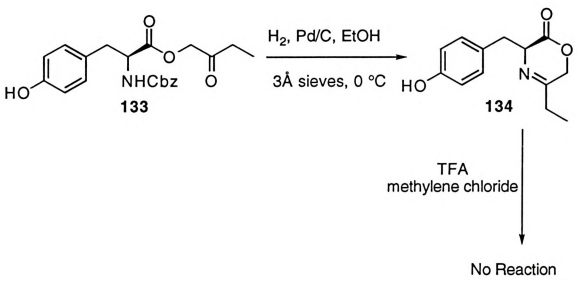


Figure 51 - Formation and Treatment of Schiff Base 134

Attempted Deamination of Tetracycle 77a

Amines are known to be very poor leaving groups. A high degree of activation is required to convert them into suitable substrates for substitution or elimination reactions.[70] While *N,N*-diarylsulfonimides are commonly employed substrates, *N*-arylsulfonamides only rarely give carbon-nitrogen cleavage. This is in sharp contrast to the behavior of alcohols, whose sulfonates are routinely employed as leaving groups (Table 2).

Table 2 - Leaving Group Comparisons

substrate structure	substrate classification	leaving group ability
$RN(SO_2Ar)_2$	*N,N*-diarylsulfonimide	good
$R_2N(SO_2Ar)$	*N*-arylsulfonamide	poor
$RO(SO_2Ar)$	arylsulfonate	good

The ease with which deamination occurs is also dependent upon the nature of the alkyl appendage of the amine.[71] For example, *N*-2-(phenylethyl)-*p*-toluenesulfonamide has been pyrolyzed with KOH to give good yields of styrene (Figure 52, eq. 1), and Mannich bases are known to undergo reverse Michael addition reactions (Figure 52, eq. 2). The driving force for these reactions is believed to be the formation of conjugated products.

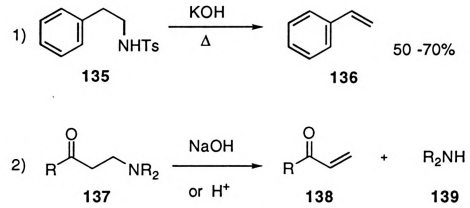


Figure 52 - Deaminations Driven by Activation of the Alkyl Appendage

Structural features unique to the tetracyclic Pictet-Spengler product **77a** prompted us to speculate that it might be induced to eliminate the previously tosylated bridging nitrogen (Figure 53). The new double bond would be conjugated with the indole ring, as well as the lactone carbonyl. The relief of ring strain in the bicyclic framework of **92** would provide an additional driving force.

Several reaction pathways exist for anionic intermediate **140**, all leading to interesting and highly functionalized products. Simple protonation would give the eight membered macrocycle **141**. Alternatively, addition of the nitrogen at the carbonyl, followed by elimination of oxygen would give a similar eight membered macrocycle **142**, while the Michael addition pathway would yield the rearranged tetracycles **143a** and **143b**.

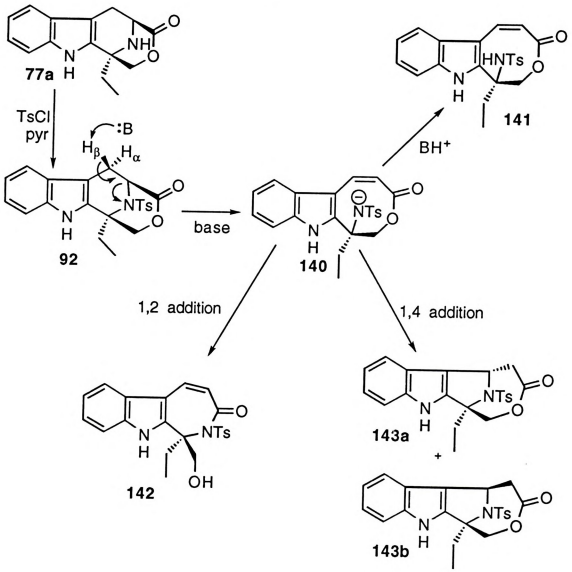


Figure 53 - Possible Deamination Pathways for 92

Computer based molecular modeling (Spartan® version 3.1, AM1, semiempirical geometry optimization, Silicon Graphics® workstation) was carried out to determine if **92** meets the stereoelectronic requirements for E2 elimination. The dihedral angle between the departing nitrogen and proton H_β was calculated to be 167°, close enough to the ideal trans periplanar arrangement to ensure that there would be sufficient orbital overlap of the developing p-orbitals of the new pi bond.

We felt that a non-nucleophilic, yet strong base should be used, to prevent attack of the strained bridged lactone. These properties have made 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) a popular choice for eliminations involving sensitive molecules.[72] Thus, we decided to employ it here.

The treatment of **77a** with *p*-toluenesulfonyl chloride in pyridine gave *p*-toluenesulfonamide **92** in a yield of 93%. When the tosylate was treated with DBU (55 eq.) in tetrahydrofuran at reflux, product **145** was isolated in a yield of 69% (Figure 54). The formation of **145** results from nucleophilic attack by DBU at the lactone carbonyl to give betaine **144**, which is hydrolyzed to **145** on aqueous workup. Reducing the amount of DBU (5.5 eq) gave the same product in lower yield. Key spectral evidence to support this assignment is the presence of two imide carbonyl bands in the IR spectrum (1646, 1622 cm^{-1}), and in the mass spectrum a parent molecular ion peak at 580 m/z, which indicates that the product is an adduct of the tosylate, DBU and water. No elimination products were isolated.

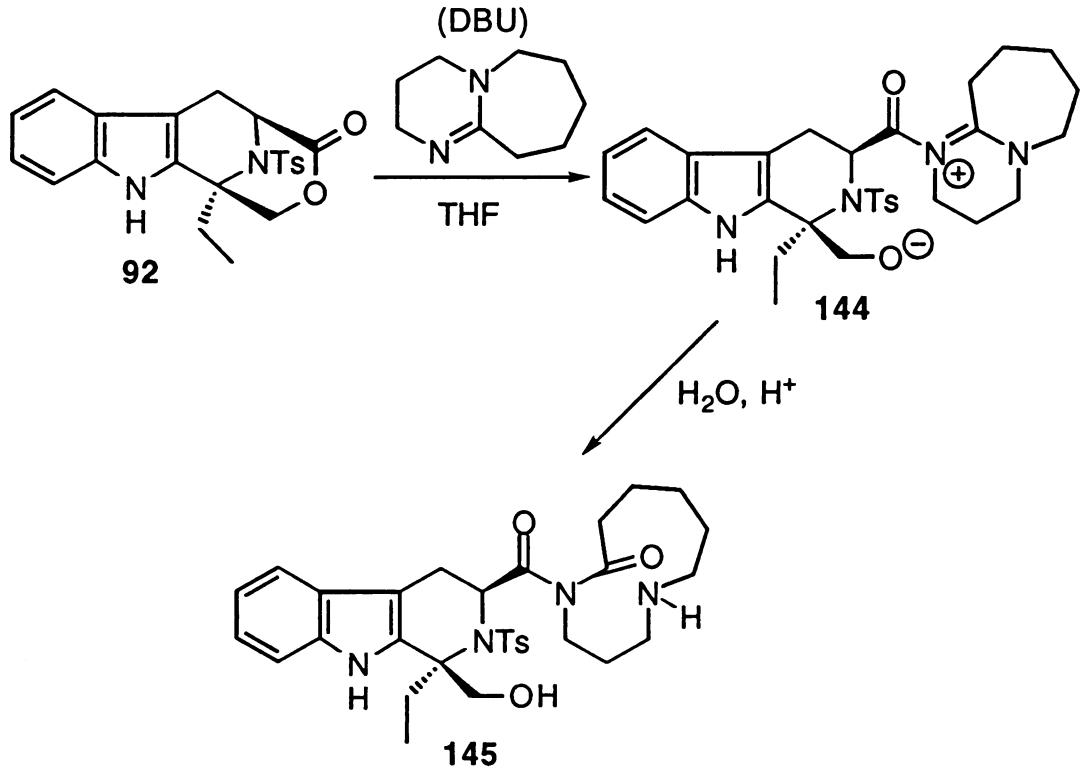


Figure 54 - Reaction of *N*-Tosylate 92 with DBU

Additional molecular modeling suggests that the rigid framework of **92** limits the degree of activation toward elimination that can be gained from conjugation of the departing groups with the indole ring or the carbonyl. In the most stable conformation of the starting material, the dihedral angle of H_β with the indole ring was calculated to be 132° (optimum orbital overlap occurs at 90° or 270°), suggesting that only moderate orbital overlap exists between the ring pi system and the breaking carbon/hydrogen bond. Also, the dihedral angle of the departing nitrogen with the carbonyl bond was calculated to be 158° (optimum orbital overlap occurs at 90° or 270°), suggesting that very little orbital overlap exists between the breaking nitrogen-carbon bond and the carbonyl pi bond. Furthermore, molecular modeling performed on elimination product **141** suggests that a geometry in which the extended pi system maintains perfect orbital overlap would result in a significantly strained eight membered ring, since in the optimized structure, conjugation of the extended pi system is significantly compromised. (Double bond/indole ring dihedral

angle = 27°. Double bond/carbonyl dihedral angle = 144°. Optimum orbital overlap occurs at 0° or 180°.)

While we were never certain that deamination of **92** would occur, we were surprised to find that nucleophilic attack of the lactone by DBU had occurred. Though renowned for its non-nucleophilic nature, a review of the literature revealed several other examples where DBU behaves as a nucleophile.[72b] The reactions illustrated in Figure 55 demonstrate that both the betaine (eq. 2) or the hydrolyzed product (eq. 1) can be isolated.

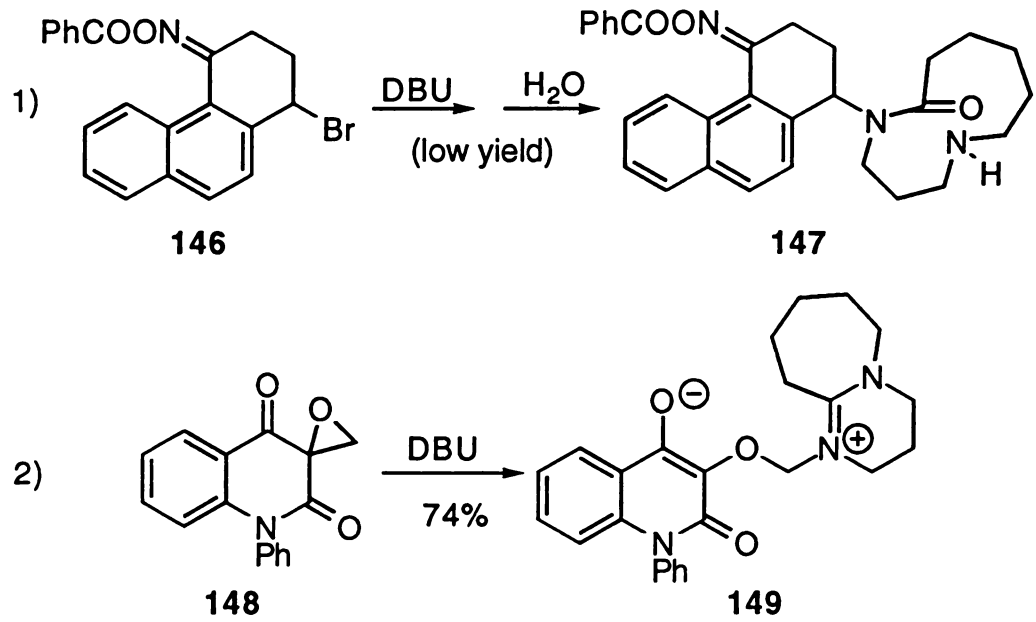


Figure 55 - Examples of Nucleophilic Behavior of DBU

The apparent hyper-sensitivity of **92** to nucleophilic cleavage of the lactone moiety, as well as the failure to isolate any elimination products in the reaction with DBU, caused us to halt our deamination efforts. However, we did gain some insight into the stability of the bridged, tetracyclic ring system generated in these intramolecular Pictet-Spengler reactions. It appears that there is sufficient ring strain present to make the cleavage of the lactone unusually facile. This has implications for the case involving the formation of **123**, which was discussed earlier (Figure 46). Whether methanolysis occurs before or after the Pictet-Spengler reaction is central to the maintenance of reaction

stereocontrol. That the lactone is so susceptible to nucleophilic cleavage agrees with the scenario in which methanolysis occurs after the Pictet-Spengler reaction, and that strain in the newly formed framework drives the cleavage.

CONCLUSION

We have demonstrated that our temporary tethering strategy for stereocontrol in the Pictet-Spengler reaction can be employed to effect the stereospecific conversion of tryptophan into THβC's bearing a new asymmetric center at the C-1 position. The exclusive formation of 1,3-cis disubstituted THβC **123a** from tethered aldehyde **103** is significant in that the configuration of the C-1 stereocenter matches that of most alkaloids containing this substructure. This also compliments the asymmetric Pictet-Spengler technology of Cook *et al.*, which gives 100% trans diastereoselectivity.

In addition to providing stereocontrol, tethering of the reaction components renders them more reactive. This makes it possible to perform asymmetric Pictet-Spengler reactions in which the carbonyl component is a ketone, resulting in the formation of an asymmetric quaternary center at the crucial C-1 of a THβC. Specifically, we achieved the transformation of *N*-protected tethered ketones **75** (Cbz protecting group) and **96** (Boc protecting group) to the bridged tetracyclic lactone **77a**, which gave the 1,1,3-trisubstituted THβC **102** upon ammonolysis.

We were unable to apply our temporary tethering strategy to the asymmetric synthesis of THIQ's from L-tyrosine, as imine **134** failed to cyclize. However, it is likely that success in this area could be achieved if the benzene ring were to bear an electron-donating group at the 3-position.

Notable among the many difficulties encountered in this study was the susceptibility of the acyl ester tethering linkage toward hydrogenolysis during removal of the *N*-Cbz protecting group. This was especially troublesome in the case of tethered aldehyde **103**.

For this reason, tethered aldehydes may be better suited for the one step deprotection/cyclization route, in which a Boc protecting group is employed.

Interesting variations of this strategy may result from the use of different protecting groups and more complex carbonyl components. Also worthy of future investigation is the elaboration of the functionalized appendages at the C-1 and C-3 positions to provide more complex alkaloids.

ADDENDUM

After the completion of this writing, we learned that Corey and coworkers had employed a strategy similar to our own as a key part of their recently reported enantioselective total synthesis of ecteinasicidin 743 (**152**, Figure 56).[73] They accomplished the conversion of acetal **150** to its corresponding aldehyde using $BF_3 \cdot Et_2O$ and H_2O (10 equivalents of each) in methylene chloride at 0 °C. Treatment of the aldehyde with $BF_3 \cdot Et_2O$ and 4Å molecular sieves in methylene chloride at 23 °C gave the bridged lactone **151** in 73% yield from the acetal. It is interesting to note that in their hands the intramolecular Pictet-Spengler reaction was carried out with the *N*-carbobenzoxy protecting group still in place.

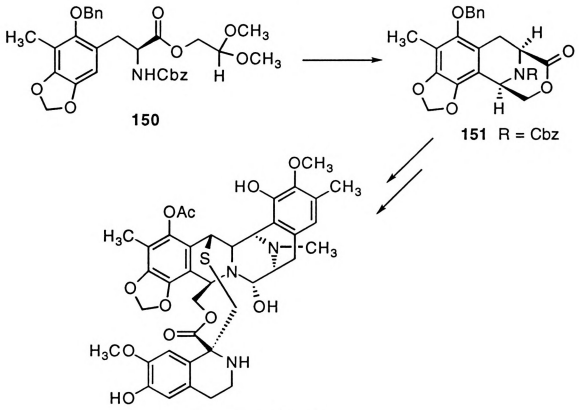


Figure 56 - Corey's Synthesis of Et 743

EXPERIMENTAL

General Methods

All reactions sensitive to moisture or oxygen were performed in oven dried glassware under an atmosphere of argon or nitrogen. Reagents were used as received from commercial suppliers unless otherwise specified. Solvents were purified by distillation from the appropriate drying reagents. Small scale reactions were stirred magnetically, and large scale reactions were agitated with paddle stirrers. Reaction progress was monitored by thin layer chromatography, with visualization by ultraviolet fluorescence, alkaline aqueous potassium permanganate, or ammonium molybdate in 10% aqueous sulfuric acid with subsequent heating. Concentration of solutions after workup was conducted on a Buchi rotary evaporator. Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh, ASTM), according to the method of Still.[74]

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or on a Reiterate hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Infrared (IR) spectra were recorded on a Nicolet PC/IR Fourier transform spectrometer, equipped with a Nicolet IR/42 optical bench. NMR spectra were obtained on Varian Gemini 300 (300 MHz), VXR-300 (300 MHz), or VXR-500 (500 MHz) spectrometers. Chemical shifts for proton signals are reported in parts per million (δ) relative to residual solvent, or to tetramethylsilane (TMS) as an internal standard. Signal splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are reported in Hertz. ^{13}C NMR data are reported as chemical shift in parts per million (δ) relative to residual solvent, or to TMS as an internal standard. Mass spectra (MS) were obtained by electron ionization (EI) on a TRIO-1 GC/MS mass spectrometer, or by fast atom bombardment

(FAB) on a JEOL-HX-110 double focusing mass spectrometer operating in the positive ion mode. High resolution mass measurements (HRMS) were carried out by EI on a JEOL-AX-505H double-focusing mass spectrometer, or by FAB as noted above.

Preparation of *N*-Cbz Protected Ester 73

To a solution of *N*-carbobenzyloxy-L-tryptophan (2.00 g, 5.91 mmol) in freshly distilled pyridine (19 mL) was added *p*-toluenesulfonyl chloride (2.25 g, 11.8 mmol) under an argon atmosphere at room temperature. This solution was cooled to 0 °C and 1-hydroxy-2-butanone (0.547 g @ 95%, 6.21 mmol) was added dropwise via syringe over a period of 10 minutes. Stirring was continued on ice for 1.5 hr at which time the contents were poured into 90 mL of ice water. The mixture was extracted with ethyl acetate, washed with 1N HCl until the washings were acidic, then with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue purified by column chromatography to give ester **73** as an oil (2.04 g, 85%). The oil was crystallized from ethanol/petroleum ether to give a white solid: mp 101-102 °C; $[\alpha]^{21}_{D} = -17°$ (*c* = 0.28 g/100 mL in methanol); IR (KBr disk) 3422, 3380, 3034, 2986, 2940, 1740, 1705 (w/ shoulder), 1524, 1217 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.3 Hz), 2.31 (2H, q, *J* = 7.3 Hz), 3.31 (1H, dd, *J* = 6.0, 14.8 Hz), 3.42 (1H, dd, *J* = 5.5, 14.8 Hz), 4.55 (1H, d, *J* = 16.6 Hz), 4.68 (1H, d, *J* = 16.6 Hz), 4.8 (1H, m), 5.0-5.1 (2H, m), 5.38 (1H, d, *J* = 8.0 Hz), 7.0-7.6 (10 H, m), 8.33 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.0, 27.7, 31.9, 54.5, 66.9, 68.1, 109.4, 111.3, 118.3, 119.5, 122.0, 123.4, 127.5, 128.0, 128.1, 128.4, 136.1, 155.8, 171.5, 204.1 ppm; MS (70 eV) m/z (relative intensity) 408 (M^+, 1.7), 130 (100), 91 (35), 77 (6.4) ppm; HRMS (EI) calcd. for $C_{23}H_{24}N_2O_5$ m/z 408.1685, found m/z 408.1686.

Preparation of Imine 75

To a 0 °C solution of *N*-protected ester **73** (O.169 g, 0.414 mmol) in 24 mL of absolute ethanol was added 0.031 g of 10% Pd/C. The solvent was degassed by alternate evacuation (aspirator) and purging with hydrogen via a gas buret hydrogenator. This was repeated three times. Hydrogenation was commenced by vigorous magnetic stirring. After 4 h the reaction mixture was filtered through celite and the solvent removed *in vacuo*. The oil obtained was then passed through a 2 inch column of flash grade silica, eluting with hexane/ethyl acetate (3/7). Removal of the solvent left 0.98 g (92%) of pure imine **75**, which crystallized on standing. Recrystallization from methanol gave white elongated platelets: mp 149-150 °C. $[\alpha]^{23}_{D} = -19°$ (c = 2.6 g/100 mL in methanol); IR (KBr disk) 3426, 3177, 2932, 1744, 1696, 1451, 1244, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (3H, t, J = 7.4 Hz), 1.8-2.1 (2H, m), 3.4-3.6 (3H, m), 4.3 (1H, dd, J = 2.0, 16.5 Hz,), 4.7 (m, 1H), 7.0 (m, 1H), 7.1(2H, m) 7.3 (1H, d, J = 8.1 Hz,), 7.6 (1H, d, J = 8.2 Hz,), 8.3 (1H, broad s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 28.5, 28.9, 60.5, 68.6, 110.4, 111.0, 119.4, 119.5, 122.1, 123.5, 127.6, 135.8, 167.4, 169.7; MS (70 eV) m/z (relative intensity) 256 (M^+, 91), 169 (7.6), 143 9 (8.6), 142 (8.6), 131 (60), 130 (100), 115 (53), 103 (60), 77 (67) ppm; HRMS (EI) calcd. for $C_{15}H_{16}N_2O_2$ m/z 256.1212, found m/z 256.1187.

Pictet-Spengler Cyclization of Imine 75

To a stirred solution of the imine **75** (0.542 g, 2.11 mmol) and methylene chloride (57 mL) at room temperature under an argon atmosphere was added trifluoroacetic acid (0.284 g, 2.49 mmol) over a period of 5 minutes. As the reaction progressed an oily precipitate formed. After 18 hours the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, then with saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Concentration of this solution *in vacuo* induced crystallization. The crystals were filtered and washed with cold ether to yield **77a** (0.374 g). Second and third crops were taken to yield an additional 0.074 g.

(Total mass 0.448 g, 83%): mp 224-225 °C; $[\alpha]^{24}_D$ = -55° (*c* = 0.20 g/100 mL in acetone); IR (KBr disk) 3285, 3195, 2986, 2936, 1721, 1449, 1179, 752 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.90 (3H, t, *J* = 7.4 Hz), 1.73 (1H, overlapping dq, *J* = 7.3, 14.1 Hz), 2.19 (1H, overlapping dq, *J* = 7.4, 14.0 Hz), 2.84 (1H, broad s), 2.92 (1H, dd, *J* = 1.5, 15.3 Hz), 3.10 (1H, dd, *J* = 5.6, 15.4 Hz), 4.18 (1H, dd, *J* = 1.6, 5.6 Hz), 4.30 (1H, d, *J* = 10.5 Hz), 4.45 (1H, d, *J* = 10.2 Hz), 7.0-7.1 (2H, m), 7.32 (1H, m), 7.44 (1H, m), 10.10 (1H, broad s) ppm; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.5 Hz), 1.73 (1H, overlapping dq, *J* = 7.3, 14.4 Hz), 1.88 (1H, broad s), 1.94 (1H, overlapping dq, *J* = 7.3, 14.4 Hz), 3.10 (2H, d, 3.6 Hz), 4.23 (1H, d, *J* = 10.5 Hz), 4.33 (1H, overlapping dd, *J* = 3.6, 3.6 Hz), 4.42 (1H, d, *J* = 10.5 Hz), 7.1-7.2 (2H, m), 7.32 (1H, m), 7.44 (1H, m), 7.90 (1H, broad s) ppm; ^{13}C NMR (75 MHz, acetone-d_6) δ 7.5, 27.3, 28.5, 52.6, 54.6, 79.5, 110.5, 112.0, 118.6, 119.8, 122.4, 127.9, 134.8, 137.4, 171.7 ppm; MS (70 eV) m/z (relative intensity) 256 (M^+, 22), 197 (100), 182 (12), 168 (4.7), 154 (6.3), 99 (6.0), 91 (12), 77 (4.6) ppm; HRMS (EI) calcd. for $C_{15}H_{16}N_2O_2$ m/z 256.1212, found m/z 256.1194

Preparation of *N*-Boc Protected Ester 96

In a dry, 100 mL round bottom flask under argon, *N*-(*tert*-butoxycarbonyl)-L-tryptophan (3.90 g, 12.8 mmol) was dissolved in pyridine (41 mL). To this solution was added *p*-toluenesulfonyl chloride (4.89 g, 25.6 mmol), which caused the solution to turn a bright yellow color. The flask was placed in an ice bath and 1-hydroxy-2-butanone (Aldrich 95%, 1.18 g, 13.4 mmol) was added via syringe over a period of 45 minutes. After stirring for 9 hours the contents were poured into 150 mL of ice water and extracted with ethyl acetate. The organic extract was washed with water, then with saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* to give an oily residue contaminated with a small quantity of precipitated material which was insoluble in ethyl acetate. The residue was filtered through a plug of silica, eluting with ethyl acetate, and the solvent removed *in vacuo* to give ester **96** (2.87 g, 60%)

as a foam. Recrystallization from ethyl acetate/hexane produced a white powder: mp 80-81 °C; $[\alpha]^{23}_D$ = -4.2° (*c* = 0.26 g/100 mL in methylene chloride); IR (NaCl thin film) 3382 (br), 2978, 2936, 1751, 1729, 1700, 1503, 1368, 1165, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.3 Hz), 2.33 (2H, 2 q, overlapping, J = 7.3 Hz), 3.29 (1H, dd, *J* = 6.0, 14.9 Hz), 3.39 (1H, dd, *J* = 5.5, 14.8 Hz), 4.53 (1H, d, *J* = 16.8 Hz), 4.68 (1H, d, *J* = 16.8 Hz), 4.7-4.8 (1H, m), 5.06 (1H, d, *J* = 8.0 Hz), 7.1-7.2 (3H, m), 7.32 (1H, d, 7.4 Hz), 7.56 (1H, d, 7.7 Hz), 8.31 (1H, broad s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.0, 27.8, 28.3, 32.0, 54.2, 68.1, 80.0, 109.7, 111.2, 118.6, 119.6, 122.1, 123.3, 127.7, 136.1, 155.3, 171.9, 204.4 ppm; MS (70 eV) m/z (relative intensity) 374 (M^+, 0.53), 318 (1.0), 257 (1.3), 159 (9.1), 141 (8.6), 130 (100), 86 (28), 84 (42), 71 (23); HRMS (EI) calcd. for $C_{20}H_{26}N_2O_5$ m/z 374.1842, found m/z 374.1817.

One-Step Deprotection and Pictet-Spengler Cyclization of 96

To a stirred solution of *N*-Boc protected ester **96** (0.100 g, 0.267 mmol) in methylene chloride (10 mL) at room temperature under an argon atmosphere was added dimethyl sulfide (0.0166 g, 0.267 mmol), then trifluoroacetic acid (0.200 mL, 2.96 g, 2.60 mmol). Stirring was continued for 2 days, at which time the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and shaken with 3% NH_4OH solution, and the organic layer dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography to give **77a** (0.041 g, 60%)

Preparation of Amide 100

A 5 mL tear drop flask was charged with bridged lactone **77a** (42 mg), flushed with nitrogen, and cooled in an ice bath. The solid was then dissolved in a saturated solution of ammonia in methanol (3.5 mL, 0 °C), and sealed with a rubber septa. The flask was placed in a freezer (-10 °C) overnight, then vented with a needle and allowed to come to room temperature. Removal of the solvent *in vacuo* yielded pure amide **100** (45 mg,

100 %) as an oil: $[\alpha]^{23}_D = -103°$ (c = 0.45 g/100 mL in acetone); IR (NaCl thin film) 3414 and 3291 (broad, overlapping), 2969, 2932, 2880, 1671, 1620 and 1578 (broad, overlapping), 1462, 1410, 1302, 1055, 745 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.96 (3H, t, J = 7.5 Hz), 1.8-1.9 (2H, m), 2.62 (1H, dd, J = 11.0, 15.2 Hz), 3.10 (1H, dd, J = 4.4, 15.2 Hz), 3.61 (1H, d, J = 10.5 Hz), 3.75 (1H, dd, J = 4.4, 11.0 Hz), 3.97 (1H, d, J = 10.8 Hz), 6.62 (1H, broad s), 6.9-7.1 (2H, m), 7.3 (1H, broad s, overlapping), 7.31 (1H, d, overlapping, J = 7.5 Hz), 7.42 (1H, dd, J = 0.6, 7.5 Hz), 9.88 (1H, broad s) ppm; ^{13}C NMR (75 MHz, acetone-d_6) δ 8.8, 26.5, 30.1 (overlapping with solvent signal), 54.3, 59.0, 67.5, 109.4, 111.8, 118.4, 119.3, 121.6, 128.1, 137.4, 139.1, 176.5 ppm; MS (21 eV) m/z (relative intensity) 256 (M^+ - NH_3 or OH, 2.9), 242 (100), 197 (98), 182 (35), 181 (21), 169 (7.2), 144 (7.6), 130 (5.9); MS (FAB^+ in glycerol matrix) m/z (relative intensity) 274 (MH^+, 100), 244 (11), 242 (58), 200 (14), 197 (29), 184 (19), 182 (11), 130 (9.8) ; HRMS (FAB^+) calcd. MH^+ for $[C_{15}H_{20}N_3O]^+$ m/z 274.1555, found m/z 274.1563.

Preparation of *N*-Cbz Protected Allyl Ester 103

N-carbobenzyloxy-L-tryptophan (2.66 g, 7.85 mmol) was reacted with p-toluenesulfonyl chloride (3.38 g, 17.74 mmol) and allyl alcohol (0.541 g, 9.31 mmol) in pyridine (25.4 mL) as described above for the preparation of **73** to give, on recrystallization from ether, allyl ester **103** (2.58 g, 87%): mp 88-89 °C; $[\alpha]^{21}_D = -17°$ (c = 0.23 g/100 mL in methanol); IR (KBr disk) 3366, 1740, 1707, 1618, 1528, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.30 (2H, d, J = 5.5 Hz), 4.54 (2H, d, J = 5.5 Hz), 4.7 (1H, m), 5.0-5.1 (2H, m), 5.2-5.3 (2H, m), 5.36 (1H, d, J = 8.2 Hz), 5.7-5.9 (1H, m), 6.9-7.5 (10H, m), 8.17 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 54.6, 66.0, 66.9, 109.7, 111.3, 118.6, 118.8, 119.6, 122.2, 122.9, 127.5, 128.09, 128.14, 128.5, 131.5, 136.1, 136.3, 155.8, 171.7 ppm; MS (70 eV) m/z (relative intensity) 378 (M^+, 3.5), 130 (100), 1439 (3.9), 103 (4.4) 91 (24), 77 (9.6) ppm; HRMS (EI) calcd. for $C_{22}H_{22}N_2O_4$ m/z 378.1579, found m/z 378.1571.

Preparation of Diol 104

In a 250 mL 3-neck flask equipped with a mechanical stirrer was dissolved allyl ester **103** (1.61 g, 4.26 mmol) in 36 mL of *t*-butanol. Water (36 mL) was then added followed by potassium ferricyanide (4.16 g, 12.6 mmol), potassium carbonate (1.74 g, 12.6 mmol), 1,4-diazabicyclo[2.2.2]octane (0.238 g, 2.12 mmol), and finally 2 mL of 0.05M osmium tetroxide/t-butanol solution (0.100 mmol). The mixture was stirred vigorously at room temperature for 5 hours, at which time TLC showed an absence of starting material. Sodium sulfite (3.2 g) was added and stirring continued for 1 hour. The reaction mixture was extracted with ethyl acetate repeatedly and the organic layers dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography to yield, as an oil, diol **104** (1.16 g, 66%) as a mixture of diastereomers: $[\alpha]^{23}_{D} = +8.6°$ (c = 0.49g/100 mL in methylene chloride, for diastereomeric mixture); IR (NaCl, thin film, isomeric mixture) 3409 (br), 3059, 2951, 1701 (br), 1518, 1456, 1265, 1213, 1055, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (for major isomer) 2.0-2.2 (1H, m, D_2O exchangeable), 2.5-2.6 (1H, m, D_2O exchangeable), 3.2-3.7 (5H, m), 4.0-4.1 (2H, m), 4.6-4.7 (1H, m), 5.0-5.1 2H, m), 5.36 (1H, d, J = 7.5 Hz, D_2O exchangeable), 7.0-7.6 10 H, m), 8.17 (1H, broad s, D_2O exchangeable) ppm (* spectrum looks significantly different at higher concentrations); ^{13}C NMR (75 MHz, $CDCl_3$) δ (for major isomer) 27.8, 54.9, 62.9, 66.0, 67.1, 69.7, 109.4, 111.4, 118.4, 119.6, 122.2, 123.2, 127.3, 128.1, 128.2, 128.5, 136.0, 136.1, 156.2, 172.3 ppm; MS (20 eV) m/z (relative intensity) 412 (M^+, 4.7), 304 (3.1), 261 (4.6), 230 (3.9), 185 (3.3), 130 (100), 108 (9.6), 107 (6.5); HRMS (EI) calcd. for $C_{22}H_{24}N_2O_6$ m/z 412.1634, found m/z 412.1633.

Preparation of Aldehyde 101

The mixture of diastereomeric diols **104** obtained above (0.960 g, 2.33 mmol) was dissolved, under argon at room temperature, in 34 mL degassed acetone. To this solution was added 24 mL of degassed water, followed by the dropwise addition of a solution of sodium metaperiodate (0.697 g, 3.26 mmol, in 10 mL of water) over a period of 1 hour and 45 minutes, during which time a white precipitate began to form. Stirring was continued for an additional 22 hours, at which time the contents were poured into 425 mL of water. The mixture was extracted repeatedly with ethyl acetate and the organic layers dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography to give aldehyde **101** (0.700 g, 79%) as an oil, along with unreacted starting material **104** (0.11 g, 11%). The oil crystallized with difficulty from methylene chloride/petroleum ether to give a white solid: mp 93-97 °C; $[\alpha]^{24}_{D} = -2°$ (c = 0.51 g/100 mL in ethyl acetate); IR (KBr disk) 3378, 3059, 2932, 1756, 1736, 1715, 1531, 1213., 1188, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.3–3.4 (2H, m), 4.53 (1H, d, J = 17.4 Hz), 4.64 (1H, d, J = 17.4 Hz), 4.8 (1H, m), 5.0 (2H, m), 5.34 (1H, d, J = 8.1 Hz), 7.0-7.3 (9H, m), 7.53 (1H, d, J = 7.5 Hz), 8.18 (1H, s), 9.35 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 54.5, 67.0, 109.3, 111.3, 118.4, 119.7, 122.3, 123.2, 127.4, 128.1, 128.2, 128.5, 136.1, 155.8, 171.6, 195.3 ppm; MS (20 eV) m/z (relative intensity) 380 (M^+, 2.32), 130 (100), 108 (8.1), 107 (5.1), 91 (7.6); HRMS (EI) calcd. for $C_{21}H_{20}N_2O_5$ m/z 380.1372, found m/z 380.1380.

Preparation of *N*-Cbz Protected Methyl Acetal 109

To a solution of aldehyde **101** (0.34 g, 0.89 mmol), methanol (3.0 mL), and trimethylorthoformate (3.0 mL) was added *para*-toluenesulfonic acid (5 mg, 0.026 mmol). The solution was stirred under argon for 1 hour and 10 minutes at room temperature, then poured into ether (16 mL) and washed first with a 1:1 mixture of 5% sodium hydroxide solution and brine, then with water, and dried with anhydrous sodium sulfate. *In vacuo* removal of the solvent and purification via flash column chromatography gave methyl acetal

109 (0.289 g, 76%) as an oil: $[\alpha]^{23}_D = +17°$ (c = 0.72 g/100 mL in methylene chloride); IR (NaCl thin film) 3349 (br), 2938, 1743 and 1709 overlapping, 1513, 1457, 1193, 1135, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (3H, s), 3.33 (3H, s), 3.33 m (2H, m, overlapping), 4.07 (2H, d, J = 5.1 Hz), 4.42 (1H, dd, overlapping, J = 5.1, 5.7 Hz), 4.74 (1H, m), 5.0-5.1 (2H, m), 5.29 (1H, d, J = 8.4 Hz), 7.00 (1H, d, J = 2.1 Hz), 7.07 (1H, t, J = 7.4 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.3-7.4 (6H, m), 7.51 (1H, d J = 7.5 Hz), 8.6 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.81, 53.81, 54.16, 54.59, 63.74, 66.88, 101.03, 109.53, 111.23, 118.50, 119.61, 122.12, 123.04, 127.54, 128.06, 128.11, 128.46, 136.08, 136.20, 155.78, 171.64 ppm; MS (70 eV) m/z (relative intensity) 426 (M^+, 0.72), 394 (0.80), 318 (1.65), 1,57 (1.01), 130 (100), 108 (7.36), 91 (81), 75 (17); HRMS (EI) calcd. for $C_{23}H_{26}N_2O_6$ m/z 426.2791, found m/z 426.1771.

Deprotection of Methyl Acetal 109

To a solution of *N*-carbobenzoxy protected methyl acetal **109** (0.231 g, 0.542 mmol) in ethanol (31 mL) was added 10% Pd/C (0.039 g, 0.037 mmol Pd). The solvent was degassed and hydrogen introduced by alternate evacuation (aspirator) and purging by way of a three-way stopcock equipped with a balloon filled with hydrogen. The solution was stirred magnetically at room temperature for 2.5 hours. The catalyst was removed by filtration and the solvent removed in vacuo to yield deprotected methyl acetal **111** (0.153 g, 97%) as an oil: $[\alpha]^{23}_D = -18°$ (c = 0.11 g/100 mL in acetone); IR (NaCl thin film) 3368 (br), 3173 (br), 3055, 2926, 2836, 1740, 1588, 1458, 1342, 1190, 1134, 1074, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (2H, broad s), 3.05 (1H, dd, J = 7.5, 14.5 Hz), 3.26 (1H, dd, J = 5.1, 14.4 Hz), 3.34, (3H, s), 3.35 (3H, s), 3.84 (1H, dd, J = 5.2, 7.4 Hz), 4.12 (2H, d, J = 5.4 Hz), 4.47 (1H, overlapping dd, J = 5.3, 5.3 Hz), 6.99 (1H, d, J = 2.2 Hz), 7.1-7.2 (2H, m), 7.30 (1H, d, J = 8.0 Hz),7.60 (1H, d, J = 7.7 Hz), 8.57 (1H, broad s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 53.5, 53.6, 54.6, 62.9, 100.8, 110.3, 110.8, 118.3, 119.0, 121.6, 122.8, 127.1, 135.9, 174.7 ppm; MS (70 eV) m/z (relative intensity) 292 (M^+,9.8), 204 (1.1), 159 (9.6), 158 (5.5), 130 (100), 103 (8.2),

77 (7.0), 75 (38); HRMS (EI) calcd. for $C_{15}H_{20}N_2O_4$ m/z 292.1423, found m/z 292.1425.

Preparation of *N*-Cbz Protected Ethyl Acetal 110

To a solution of aldehyde **101** (0.681 g, 1.79 mmol) in 10 mL absolute ethanol was added 10 mL triethylorthoformate, followed by *p*-toluenesulfonic acid (0.014 g, 0.074 mmol). After stirring at room temperature for 2.5 hours the solution was poured into 100 mL of ether and washed first with a 1:1 mixture of 5% sodium hydroxide solution and brine, then with water, and dried with anhydrous sodium sulfate. *In vacuo* removal of the solvent and purification via flash column chromatography gave ethyl acetal **110** (0.647 g, 80%) as an oil: $[\alpha]^{23}_D = +17°$ (c = 0.72 g/100 mL in methylene chloride); IR (NaCl thin film) 3351 (br), 2977, 1717 (br), 1507, 1456, 1206, 1132, 1063, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, t, *J* = 7.0 Hz), 1.19 (3H, t, *J* = 7.0 Hz), 3.31 (2H, d, *J* = *5.2 Hz*), 3.4-3.6 (2H, m,), 3.6-3.7 (2H, m), 4.09, (2H, d, *J* = 5.5 Hz, 4.56) (1H, dd overlapping, *J* = 5.4, 5.4 Hz), 4.7-4.8 (1H, m), 5.0-5.1 (2H, m), 5.36 (1H, d, *J* = 8.1 Hz), 6.98 (1H, d, *J* = 1.9 Hz), 7.07 (1H, t, *J* = 7.4 Hz), 7.16 (1H, t, *J* = 7.2 Hz), 7.2-7.4 (6H, m), 7.53 (1H, d, J = 7.9 Hz), 8.24 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 27.8, 54.6, 62.4, 62.8, 64.7, 66.8, 99.4, 109.6, 111.2, 118.5, 119.6, 122.1, 123.0, 127.6, 128.0, 128.1. 128.4, 128.5, 136.0. 136.2, 155.7, 171.6 ppm; MS (70 eV) m/z (relative intensity) 454 (M^+,14), 408 (18), 346 (9.4), 292 (31), 249 (5.5), 220 (12), 185 (7.4), 158 (15), 157 (15), 130 (100), 103 (95), 91 (95), 79 (26), 77 (33), 75 (57); HRMS (EI) calcd. for $C_{25}H_{30}N_2O_6$ m/z 454.2104, found m/z 454.2119.

Deprotection of Ethyl Acetal 110

To a solution of *N*-carbobenzoxy protected ethyl acetal **110** (0.638 g, 1.40 mmol) in ethanol (90 mL) was added 10% Pd/C (0.100 g, 0.094 mmol Pd). The solvent was degassed and hydrogen introduced by alternate evacuation (aspirator) and purging by way of a three-way stopcock equipped with a balloon filled with hydrogen. The solution was

stirred magnetically at room temperature for 7.5 hours. The catalyst was removed by filtration and the solvent removed in vacuo to yield deprotected ethyl acetal **112** (0.443 g, 98%) as an oil: $[\alpha]^{23}_{D} = +3.5°$ (c = 0.37 g/100 mL in methylene chloride); IR (NaCl thin film) 3364 (br), 2977, 1738, 1458, 1188, 1132, 1069, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (6H, dt, J = 1.2, 7.0 Hz), 1.66 (2H, broad s), 3.06 (1H, dd, J = 7.5,14.4 Hz), 3.27 (1H, dd, J = 5.0, 14.6 Hz), 3.5-3.6 (2H, m), 3.6-3.7 (2H, m), 3.85 (1H, dd, J = 5.0, 7.4 Hz), 4.11 (2H, d, J = 5.5 Hz), 4.59 (1H, dd, overlapping, J = 5.4, 5.4 Hz), 7.0-7.2 (3H, m), 7.32 (1H, d, J = 7.9 Hz), 7.61 (1H, d, J = 7.5 Hz), 8.3 (1H, broad s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 30.6, 55.0, 62.4, 62.5, 64.3, 99.5, 111.0, 111.2, 118.7, 119.5, 122.1, 123.0, 127.5, 136.2, 175.1 ppm; MS (70 eV) m/z (relative intensity) 320 (M^+,1.2), 232 (3.8), 159 (8.3), 149 (5.3), 130 (100), 111 (5.2), 83 (8.5), 77 (7.9), 71 (13); HRMS (EI) calcd. for $C_{17}H_{24}N_2O_4$ m/z 320.1736, found m/z 320.1734.

Preparation of 123a from Aldehyde 101

A solution of *N*-protected aldehyde **101** (1.00 g, 2.63 mmol) in methanol (500 mL) was prepared under an atmosphere of argon. The reaction vessel was placed in an ice bath, and 10% Pd/C (0.70 g, 0.66 mmol) was added, followed by the dropwise addition of 88% formic acid (21 mL) over a period of 25 minutes. The mixture was stirred for 5 hours, then trifluoroacetic acid (2.30 mL, 29.9 mmol) was added over a period of 15 minutes. The ice bath was removed and the mixture stirred slowly for an additional 4 days at room temperature. The catalyst was removed by filtration through celite, and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. Removal of the solvent *in vacuo* and purification by flash chromatography gave **123a** (0.199 g, 29%) as a white solid: mp 190-191 °C (decomposed); $[\alpha]^{23}_{D} = -118°$ (c = 0.11 g/100 mL in methanol); IR (KBr disk) 3426 (br), 3298, 3295, 2853, 1725, 1441, 1220, 1044, 731

cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 2.63 (1H, ddd, J = 2.4, 11.1, 14.7 Hz), 2.6–2.7 (1H, broad s, coalesces with H_2O and broadens over time), 2.95 (1H, ddd, J = 1.2, 4.1, 14.4 Hz), 3.6-3.7 (1H, m), 3.7-3.8 (1H, m), 3.72 (3H, s), 4.10 (1H, m), 5.00 (1H, t, J = 5.2, coalesces with H_2O over time to give a broad singlet), 6.9-7.1 (2H, m), 7.30 (1H, d, 8.1 Hz), 7.38 (1H, d, 7.8 Hz), 10.70 (1H, s) ppm; ^{13}C NMR (75 MHz, DMSO) δ 25.5, 51.8, 54.6, 55.6, 63.4, 106.8, 111.1, 117.4, 118.3, 120.6, 126.6, 124.2, 136.0, 173.2 ppm; MS (70 eV) m/z (relative intensity) 260 (M^+, 3.6), 229 (98), 228 (6.3), 169 (100), 168 (11), 154 (6.2), 130 (6.2), 115 (14); HRMS (EI) calcd. for $C_{14}H_{16}N_2O_3$ m/z 260.1161, found m/z 260.1156.

Preparation of *N*-Cbz Protected Ester 132

A solution of *N*-Cbz-L-tyrosine (2.0 g, 6.34 mmol) in freshly distilled pyridine (20 mL) was prepared under argon. To this magnetically stirred, room temperature solution was added 1-hydroxy-2-butanone (2.84 g @ 95%, 27.9 mmol), followed by the addition of *p*-toluenesulfonic acid (0.56 g, 0.29 mmol), and finally 1,3-dicyclohexylcarbodiimide (1.57 g, 7.6 mmol). After a few minutes a precipitate began to form. Stirring was continued for 24 hours, at which time glacial acetic acid (0.63 mL) was added. The mixture was for stirred 15 minutes, then placed in a refrigerator (-4 °C) overnight). The precipitated 1,3-dicyclohexylurea was removed by filtration through celite, rinsing with 10 mL of cold pyridine. The filtrate was mixed with 20 mL each of ethyl acetate and ice, and acidified with 5N hydrochloric acid. The layers were then separated, and the organic layer washed successively with water, saturated sodium bicarbonate solution, and again with water, then dried over saturated anhydrous sodium sulfate. Removal of the solvent *in vacuo* and purification with flash column chromatography gave ester **132** (1.64 g, 67%) along with a significant amount of by-product **133**.

Characteristic properties of **132**: mp 102 °C; IR (KBr disk) 3403, 3355, 1761, 1713, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, J = 7.3 Hz), 2.39 (2H, q,

J = 7.3 Hz), 3.01 (1H, dd, J = 6.6, 14.3 Hz), 3.15(1H, dd, J = 5.8, 14.2 Hz), 4.63 (1H, d, overlapping, J = 16.7 Hz), 4.74 (1H, d, overlapping, J = 16.7 Hz), 4.6-4.7 (1H, m, overlapping), 5.0-5.1 (2H, m), 5.30 (1H, d, J = 8.5 Hz), 6.02 (1H, s, concentration dependent), 6.68 (2H, d, J = 8.2 Hz), 6.99 (2H, d, J = 8.3 Hz), 7.2-7.4 (5H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1, 32.1, 37.2, 54.8, 67.1, 68.2, 115.6, 127.2, 128.1, 128.2, 128.5, 130.5, 136.0, 155.0, 155.9, 171.3, 204.1 ppm; MS (70 eV) m/z (relative intensity) 386 (MH^+, 3.2), 385 ($M^{+\cdot}$ 2.2), 342 (13), 234 (33), 147 (15), 108 (12), 107 (100), 91 (100), 77 (11) ppm.

Characteristic properties of **133**: mp 157 °C; IR (KBr disk) 3421, 3333, 3035, 2943, 1757, 1717, 1693, 1529, 1516, 1267, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 7.3 Hz), 2.38 (2H, q, J = 7.3 Hz), 3.1-3.2 (4H, m), .4.6-4.8 (4H, m), 5.06 (2H, s), 5.10 (2H, s), 5.26 (1H, d, J = 8.3 Hz), 5.35 (1H, d, J = 8.0 Hz), 6.73 (2H, d, J = 8.3 Hz), 6.88 (2H, d, J = 8.2 Hz), 7.02 (2H, d, J = 8.5 Hz), 7.15 (2H, d, J = 8.2 Hz), 7.2-7.4 (10H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.67, 31.63, 36.97, 54.17, 54.71, 66.73, 67.77, 115.25, 120.94, 126.61, 127.72, 127.83, 128.10,128.13, 130.00, 130.15, 133.26, 135.58, 148.89, 154.78, 155.34, 169.86, 170.56, 203.38, ppm; MS (FAB^+ in glycerol matrix) m/z (relative intensity) 683 (MH^+, 17), 640 (11), 639 (27), 307 (55), 289 (29), 226 (14), 197 (18), 154 (100), 138 (49), 137 (94), 136 (100), 107 (45).

Preparation of Schiff Base 134

To a 0 °C solution of *N*-protected ester **132** (O.500 g, 1.30 mmol) in 80 mL of absolute ethanol was added 0.099 g of 10% Pd/C, and 0.25 g of 3Å molecular sieves. The solvent was degassed by alternate evacuation (aspirator) and purging with hydrogen from balloon attached to a 3-way stopcock. This was repeated three times. Hydrogenation was commenced by vigorous magnetic stirring. After 5 h the reaction mixture was filtered through celite and the solvent removed *in vacuo*. To the residue was added ethyl acetate, which precipitated a white substance. The mixture was filtered through a two inch column

of silica, eluting with ethyl acetate. The filtrate was reduced *in vacuo*, and purification by flash chromatography gave, as an oil, Schiff base **134** (0.050 g, 16%): H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.5 Hz), 2.1-2.3 (2H, m), 3.11 (1H, dd, J = 4.6, 13.7 Hz), 3.31 (1H, dd, J = 4.8, 13.7 Hz), 3.54 (1H, dd, J = 1.6, 16.7 Hz), 4.39 (1H, dd, J = 2.0, 16.8 Hz), 4.62 (1H, broad s), 6.72 (2H, d, J = 8.5 Hz), 7.00 (2H, d, J = 8.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 28.5, 38.2, 60.1, 68.7, 115.3, 127.6, 131.3, 155.1, 168.1, 169.1 ppm.

Preparation of Tosylate 92

A stirred solution of **77a** (0.357 g, 1.39 mmol) and pyridine (4.5 mL) under argon was cooled in an ice bath and charged with *p*-toluenesulfonyl chloride (0.531 g, 2.79 mmol). After 1.5 h the ice bath was removed and stirring continued at room temperature for 17 h at which time additional *p*-toluenesulfonyl chloride (0.133 g, 0.70 mmol) was added to the reaction vessel. After an additional 11 h (total reaction time 28 h) TLC showed that all starting material had been consumed and the reaction mixture was poured into approximately 20 mL of ice water. The mixture was extracted with ethyl acetate and the organic portion washed with 1N HCl until the washings were acidic, then with saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography to give crystalline **92** (0.533 g, 93%). An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 262-267 °C; $[\alpha]^{23}_D$ = -34° (c = 0.24 g/100 mL in ethyl acetate); IR (KBr disk) 3407, 2924, 1728, 1466, 1331, 1157, 1082, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.0), 1.86 (1H, dq, overlapping, J = 7.3, 14.8 Hz), 2.41 (3H, s), 2.78 (1H, dq, overlapping, J = 7.1,14.7 Hz), 3.11 (2H, m), 4.11 (1H, d, J = 11.2 Hz), 4.52 (1H, d, J = 11.2 Hz), 5.01 (1H, dd, overlapping , J = 3.4, 3.4 Hz), 7.1-7.2 (3H, m), 7.32 (2H, d, J = 8.3 Hz), J = 7.4 1H, m), 7.79 (2H, d J = 8.3 Hz), 8.34 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 21.6., 24.5, 27.1, 56.6, 61.5, 76.7, 110.8, 111.4, 118.4, 120.1, 123.1, 126.0, 127.5, 130.2, 131.0, 136.5, 136.6,

145.0, 169.2 ppm; MS (70 eV) m/z (relative intensity) 410 (M^+, 9.0), 351 (1.3), 255 (35), 227 (6.2), 197 (100), 196 (9.0), 195 (15), 182 (36), 168 (10), 171 (13), 154 (13), 91 (20) ppm; HRMS (EI) calcd. for $C_{22}H_{22}N_2O_4S$ m/z 410.1300, found m/z 410.1298.

Reaction of 92 with DBU

In a 10 mL round bottom flask sealed with a rubber septa and equipped with an argon inlet was dissolved tosylate **92** (0.100 g, 0.244 mmol) in 3 mL of tetrahydrofuran, followed by the dropwise addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (2.00 mL, 13.4 mmol) was then added dropwise via syringe. The flask was then fitted with a condenser and the solution refluxed for 19 hours. The solvent was removed *in vacuo* and the residue dissolved in chloroform. The solution was washed successively with 1N HCl, water, and saturated sodium bicarbonate solution, and dried over sodium sulfate. Removal of the solvent *in vacuo* and purification with flash column chromatography gave DBU adduct **145** (0.097 g, 69%) as a glasslike solid: $[\alpha]^{23}_D = +79°$ (c = 0.81 g/100 mL in methylene chloride); IR (NaCl thin film) 3250 (broad, with shoulder at 3373), 3092, 2930, 1646, 1622, 1327, 1159, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.4), 1.1-1.3 (3H, m), 1.3-1.5 (1H, m), 1.5-1.8 (5H, m), 1.91 (1H, dq, overlapping, J = 7.2, 14.0 Hz), 2.2-2.3 (2H, m), 2.35 (3H, s), 2.4-2.5 (2H, m), 2.54 (1H, dq, overlapping, J = 7.3, 14.0 Hz), 2.8-3.0 (3H, m), 3.07 (1H, dd, J = 6.3, 15.0 Hz), 3.46 (1H, dd, J = 1.6, 15.5 Hz), 4.35 (1H, dd, J = 5.7, 13.2 Hz), 4.90 (1H, d, J = 4.8 Hz), 5.10 (1H, dd, J = 6.2, 13.5 Hz), 6.38 (1H, t, J = 6.3 Hz), 7.0-7.1 (3H, m), 7.24 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.7 Hz), 8.66 (1H, d, J = 6.6 Hz), 8.74 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 21.4, 23.1, 24.9, 25.1, 27.6, 29.6, 33.0, 35.9, 36.8, 45.6, 50.2, 58.6, 65.0, 70.4, 108.8, 111.0, 118.1, 119.3, 121.6, 126.4, 127.9, 129.3, 133.6, 136.1, 137.6, 143.3, 171.4, 176.6 ppm; MS (70 eV) m/z (relative intensity) 580 (M^+, 3.3), 562 (3.7), 408 (8.1), 395 (10.7), 226 (37), 225 (40), 211 (25), 200 (100), 197 (33), 172 (73), 154 (37), 91 (27); HRMS (FAB^+) calcd. MH^+ for $[C_{31}H_{41}N_4O_5S]^+$ m/z 581.2797, found m/z 581.2791.

APPENDIX

APPENDIX

SPECTRA

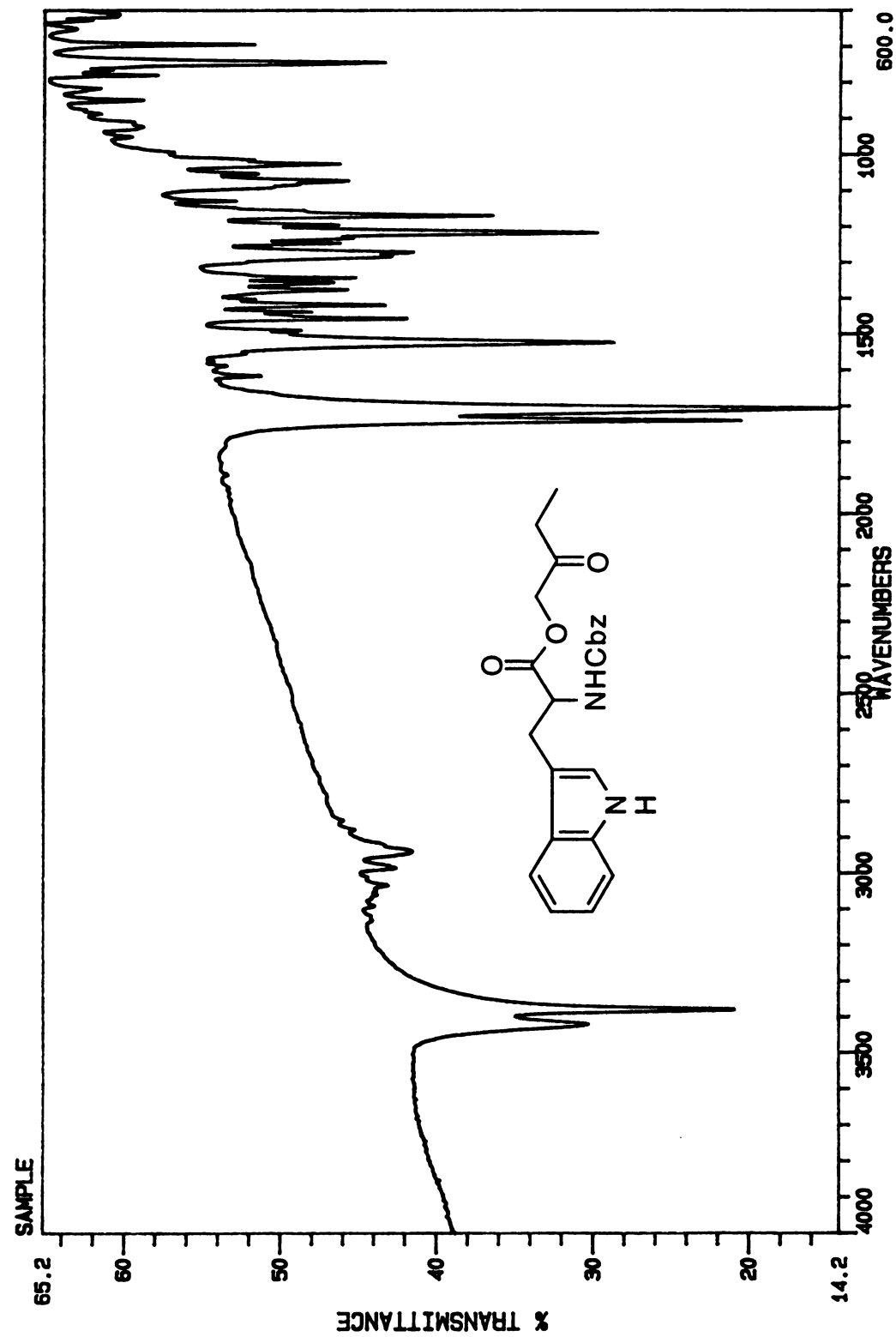


Figure 57 - IR Spectrum of 73

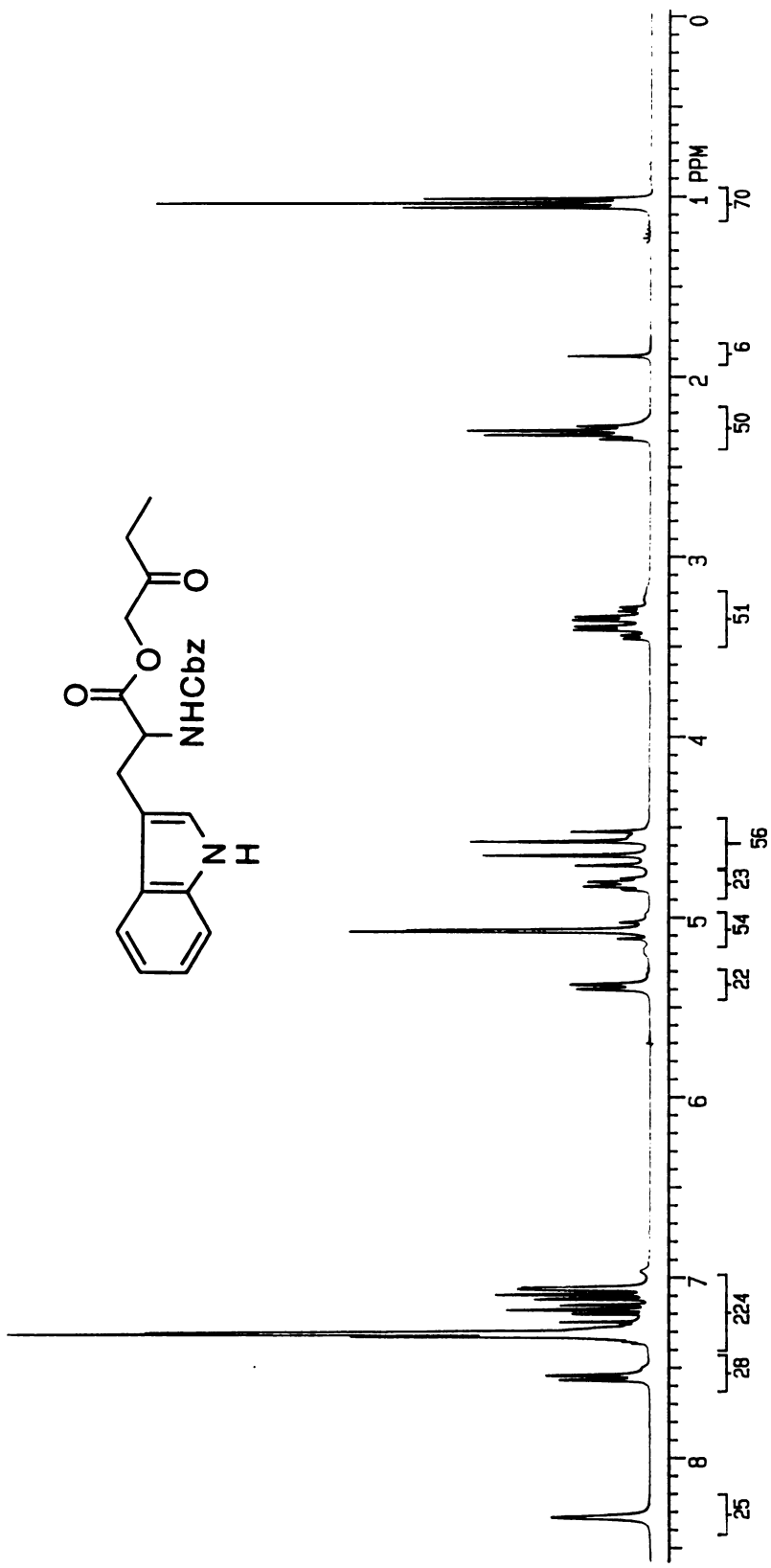


Figure 58 - ^{1}H NMR Spectrum of 73

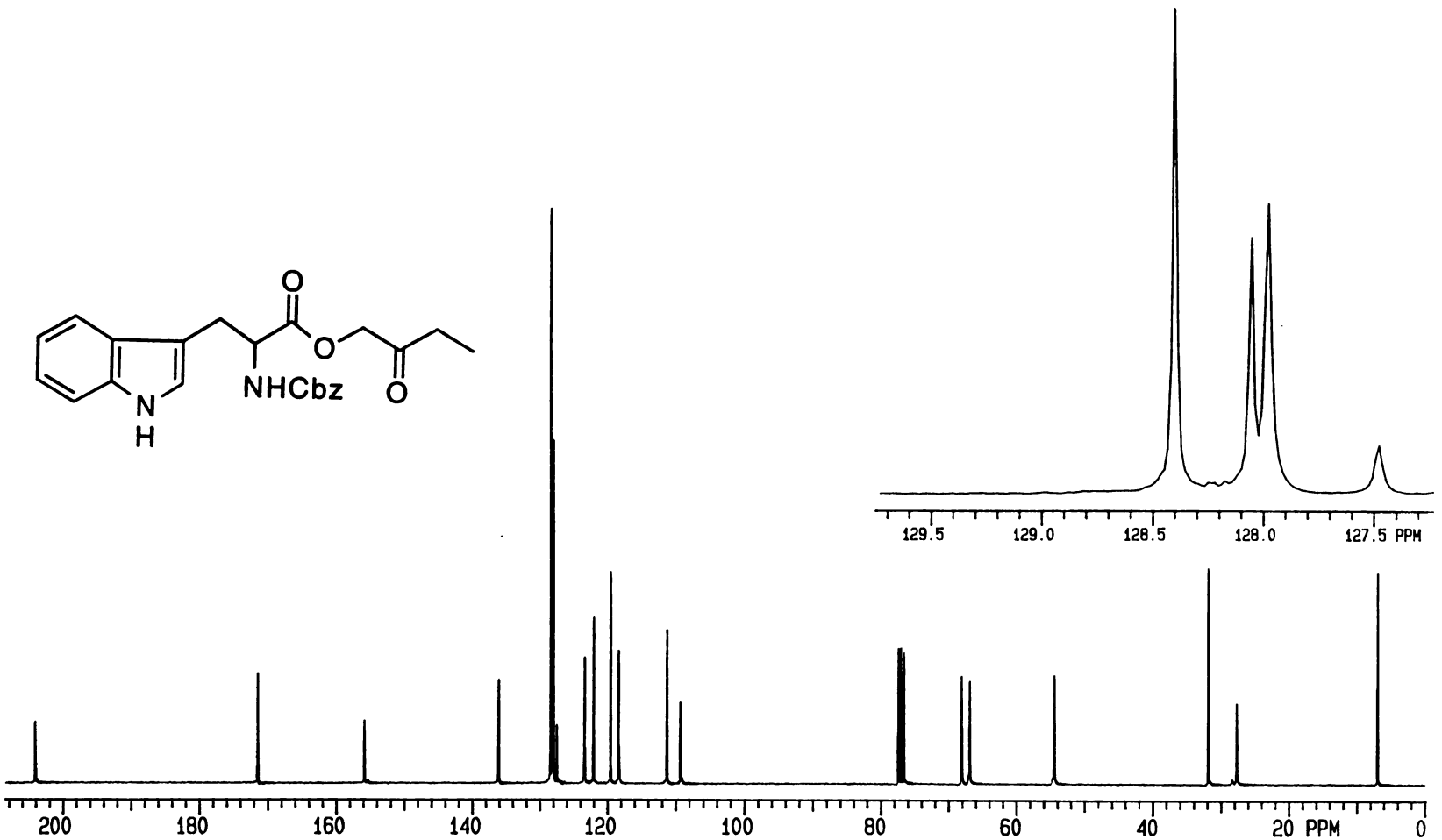


Figure 59 - ^{13}C NMR Spectrum of 73

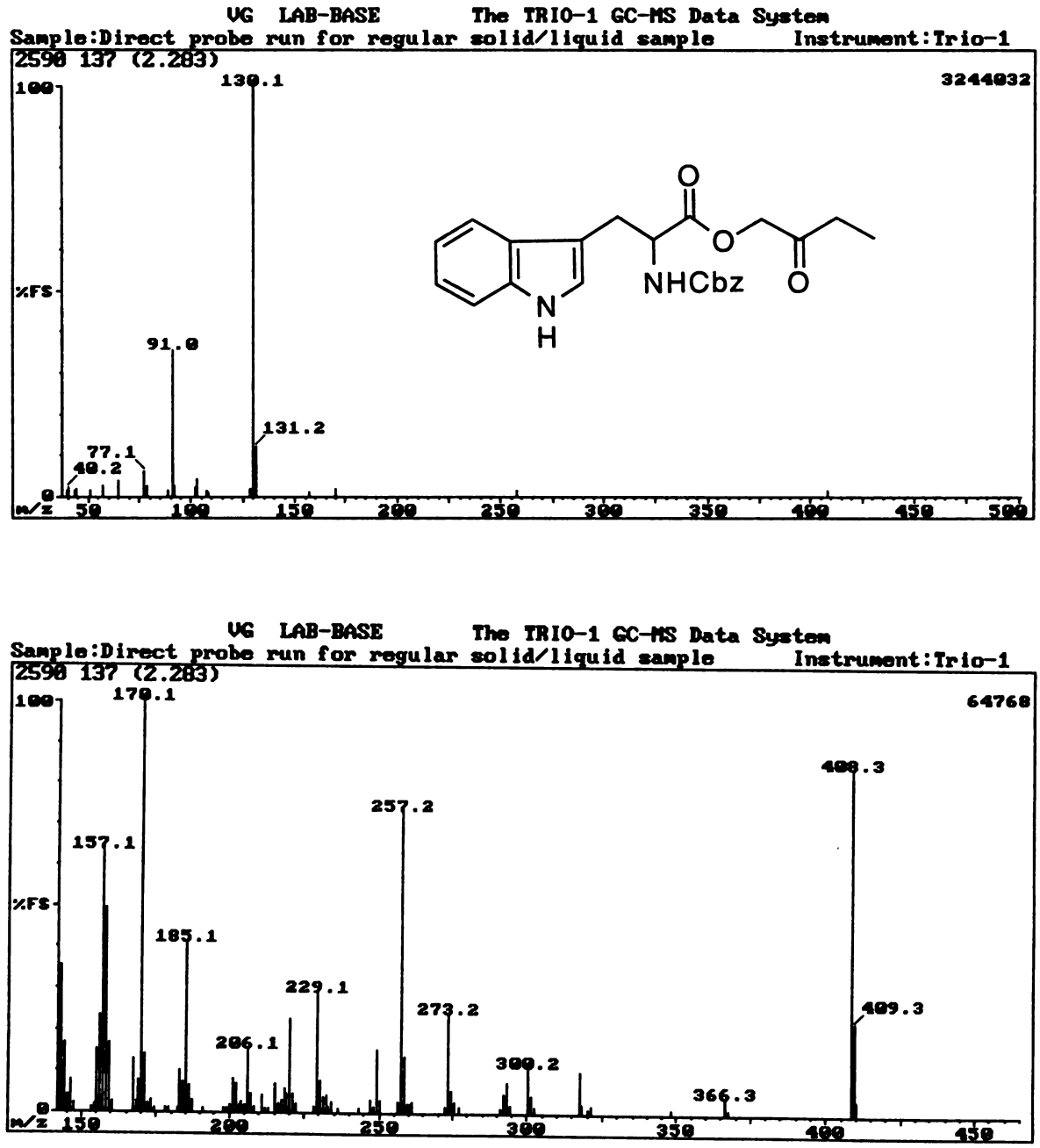


Figure 60 - Mass Spectrum of 73

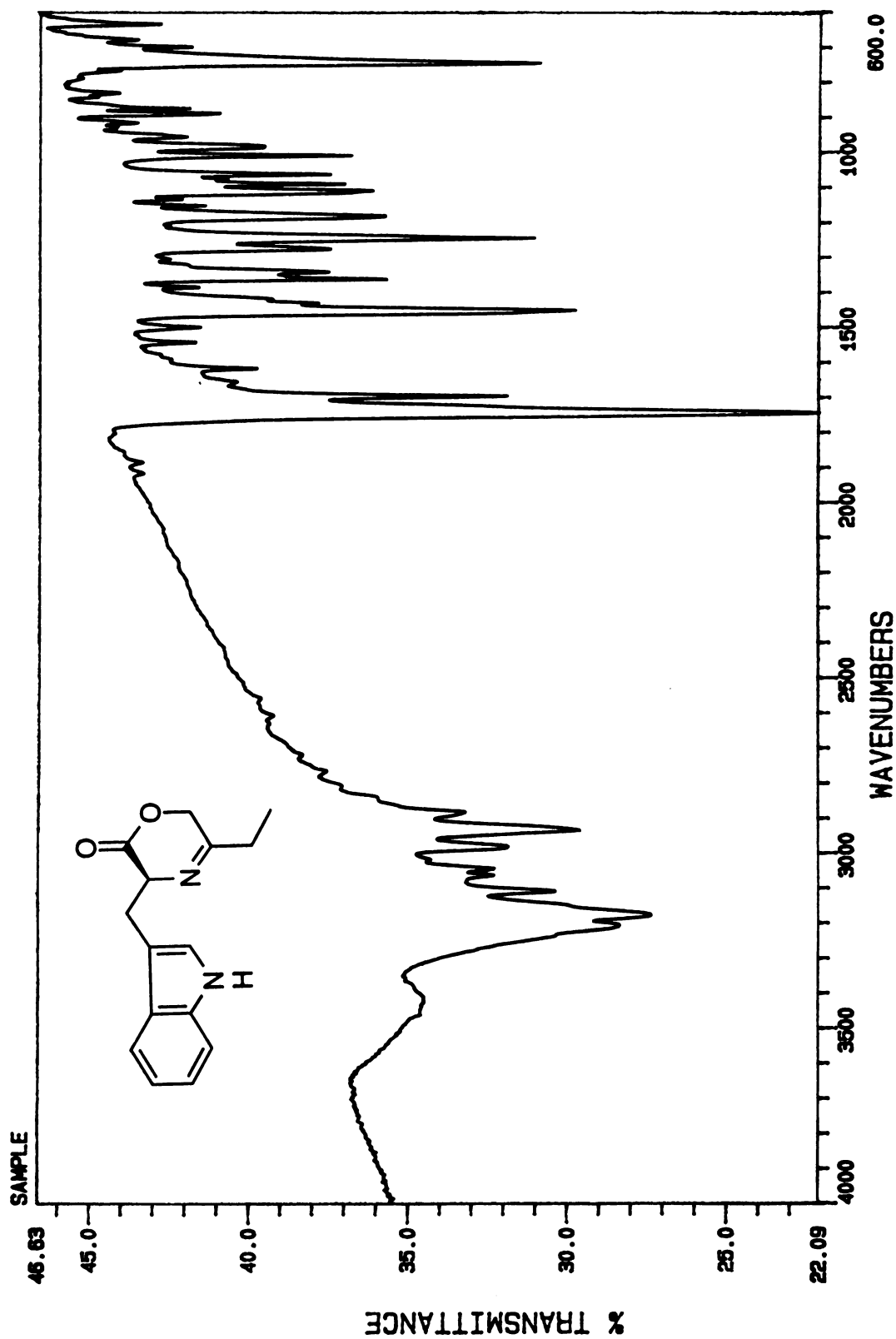


Figure 61 - IR Spectrum of 75

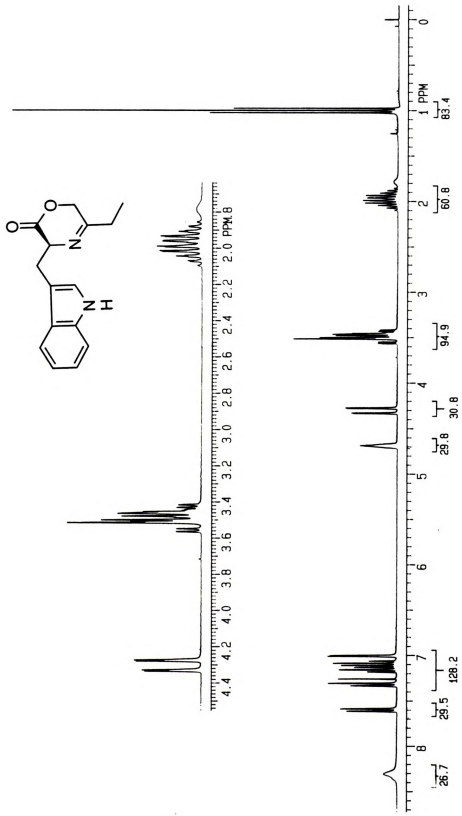


Figure 62 - ^{1}H NMR Spectrum of 75

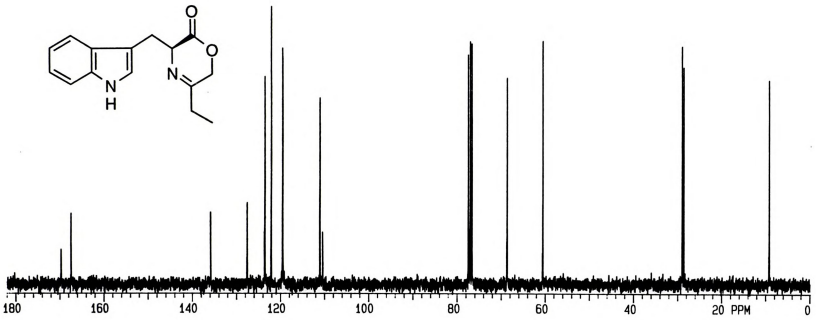


Figure 63 - ^{13}C NMR Spectrum of 75

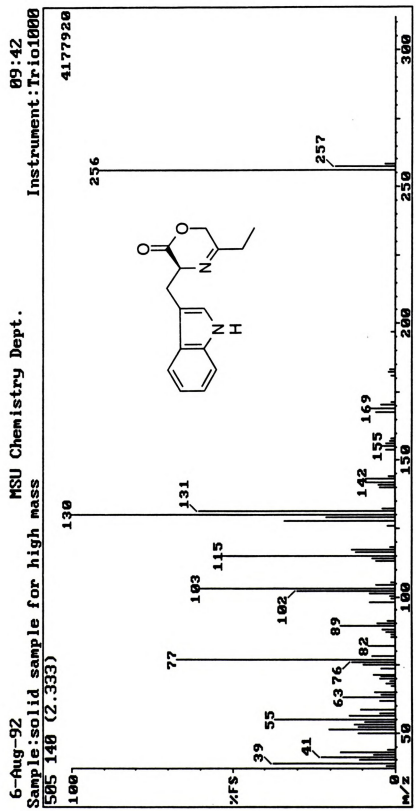


Figure 64 - Mass Spectrum of 75

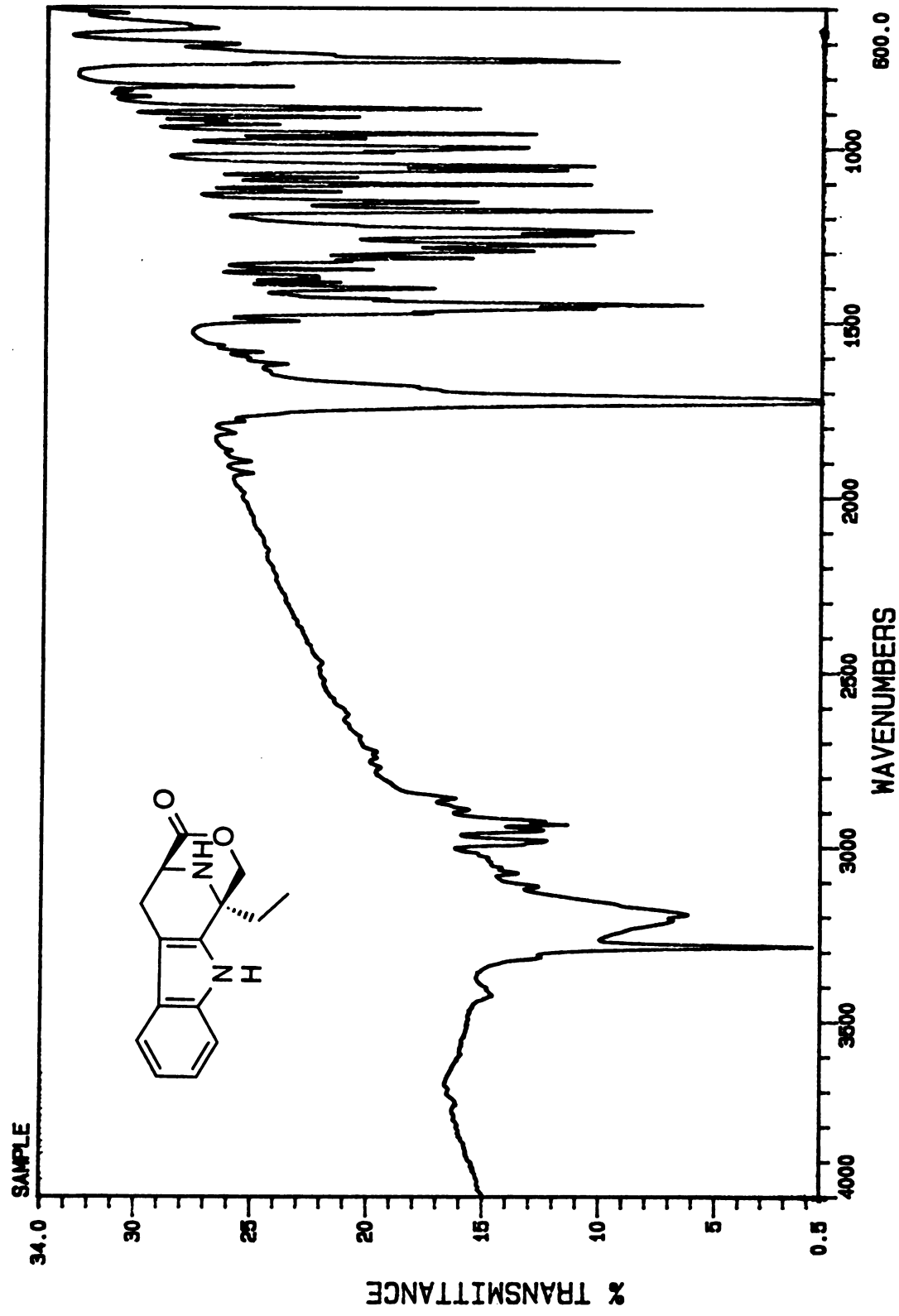


Figure 65 - IR Spectrum of 77a

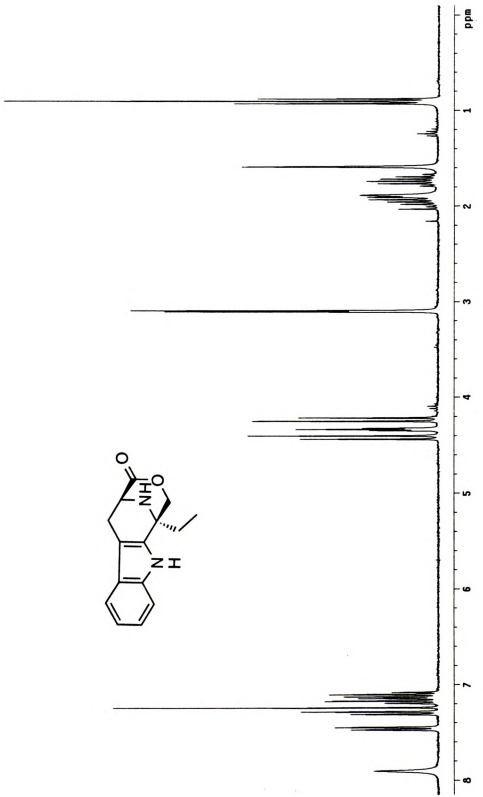


Figure 66 - ^{1}H NMR Spectrum of 77a in $CDCl_3$

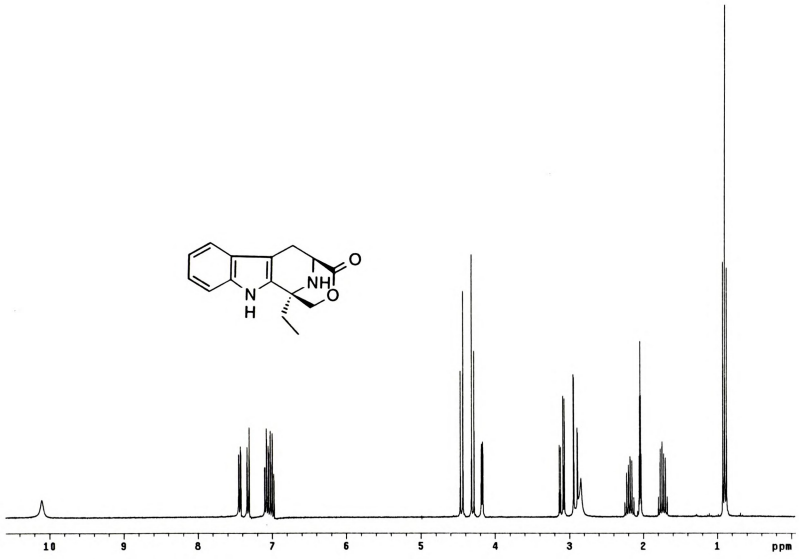


Figure 67 - ^{1}H NMR Spectrum of 77a in Acetone-d_6

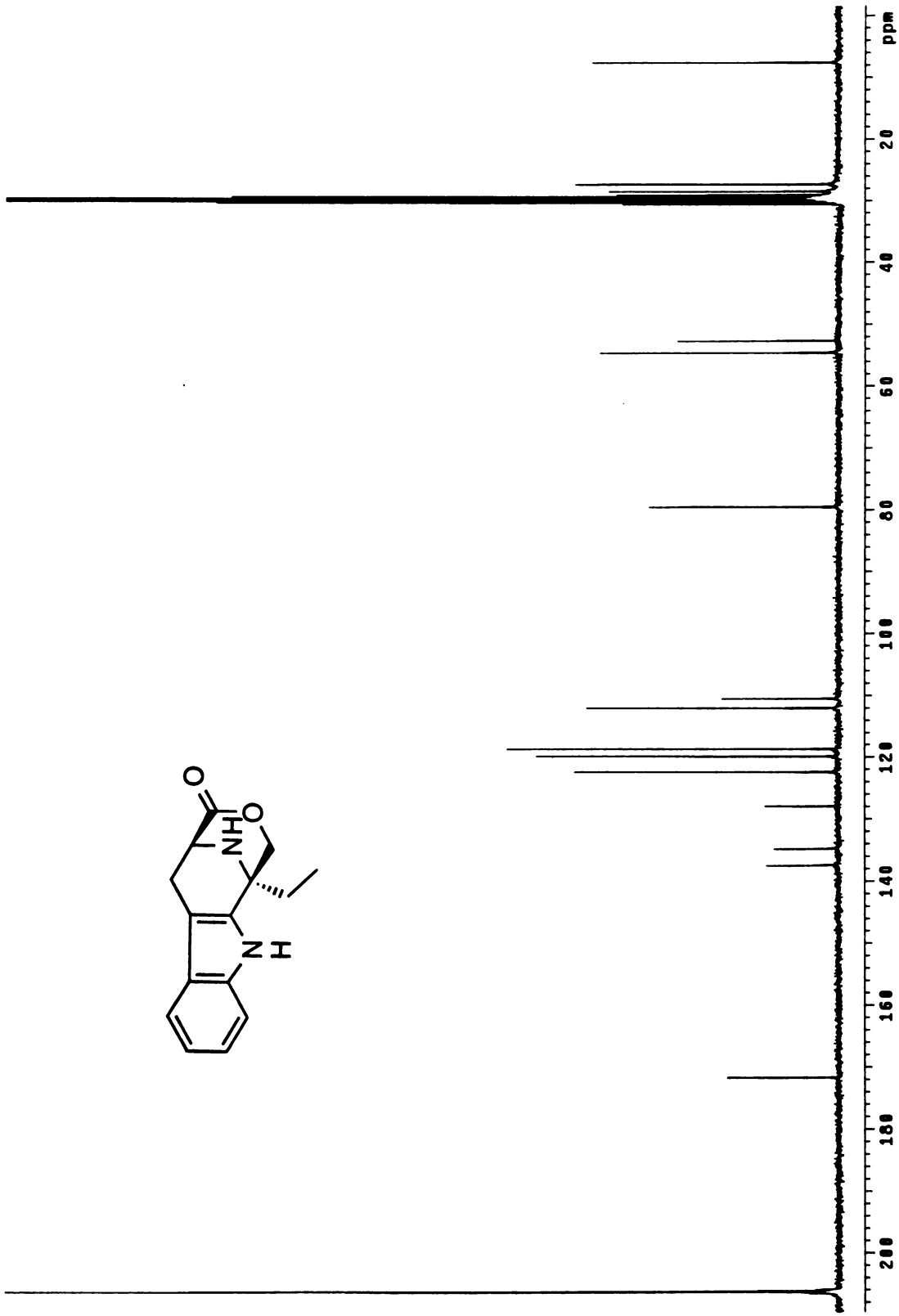


Figure 68 - ^{13}C NMR Spectrum of 77a

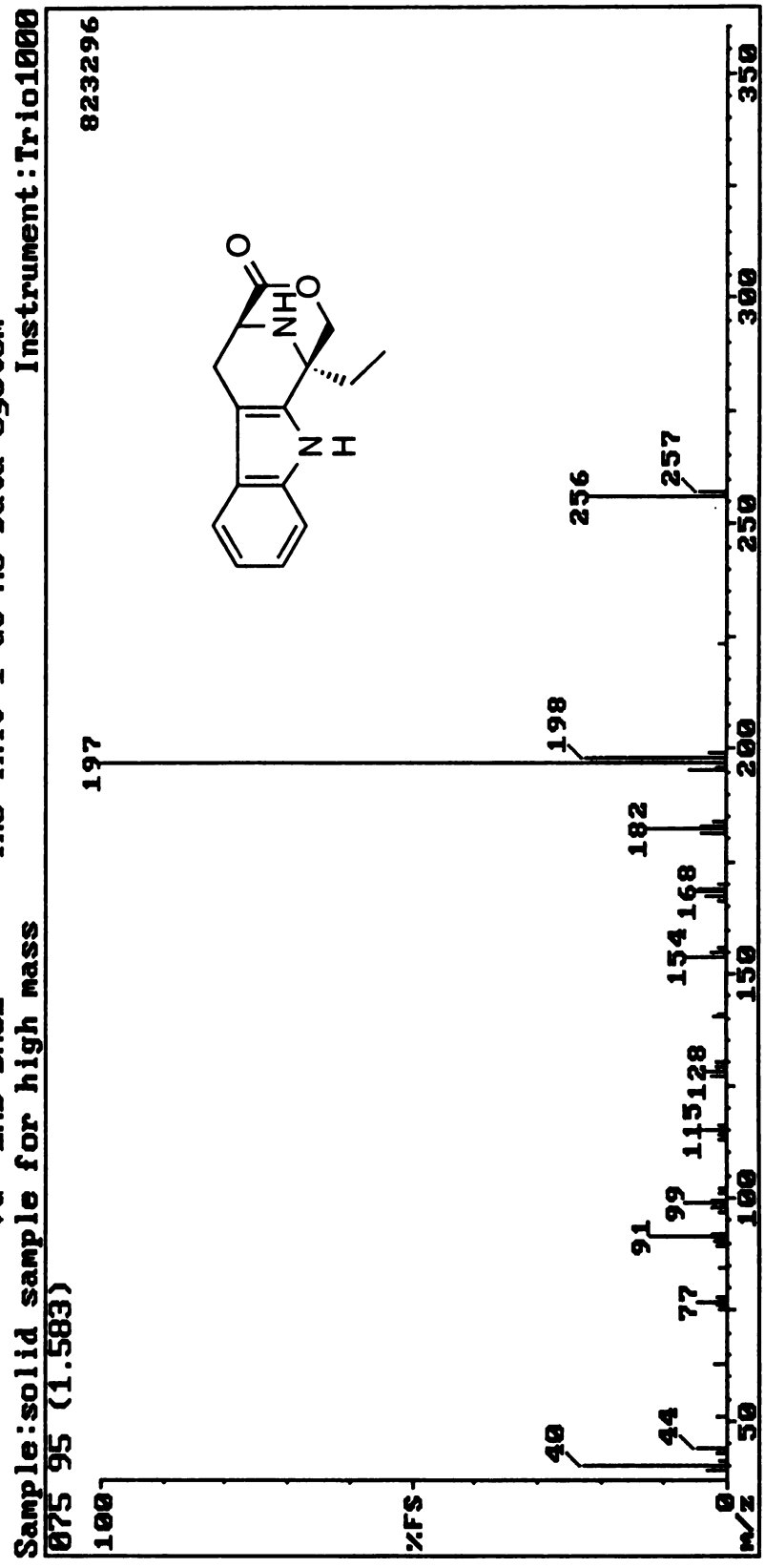


Figure 69 - Mass Spectrum of 77a

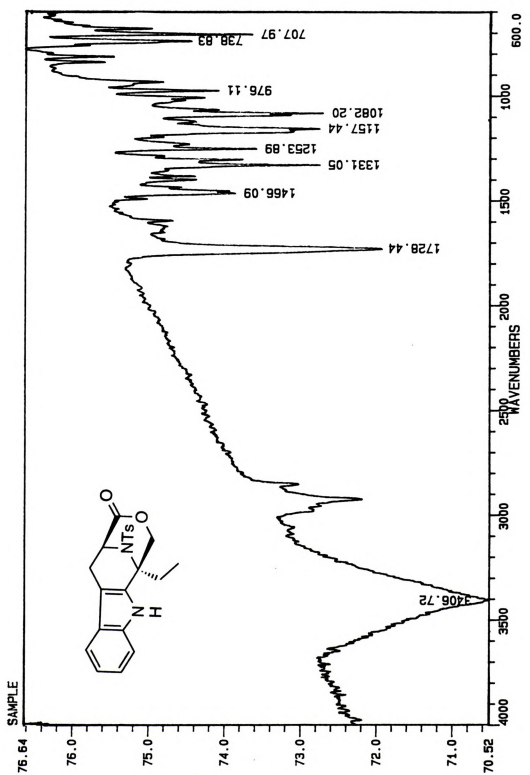


Figure 70 - IR Spectrum of 92

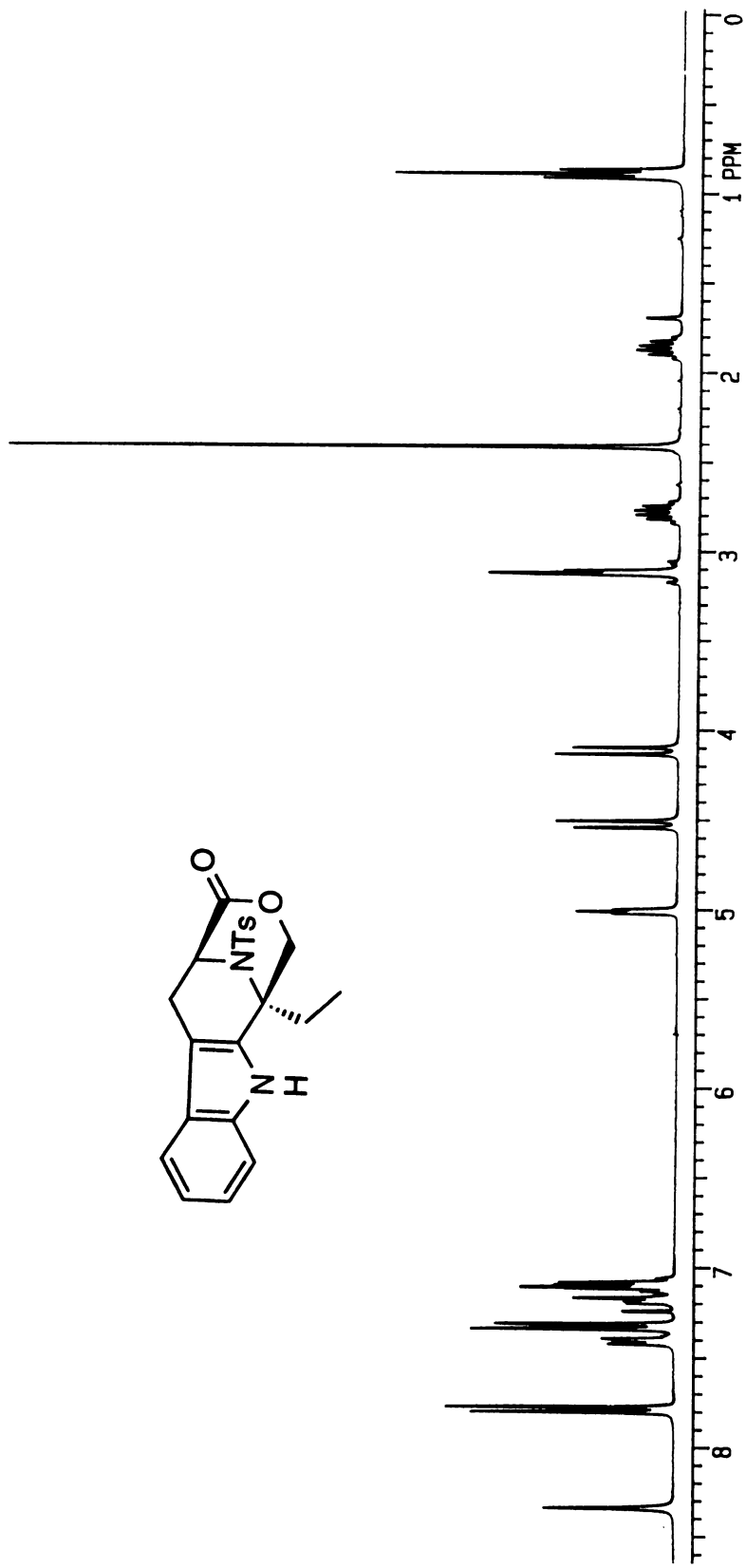


Figure 71 - ^{1}H NMR Spectrum of 92

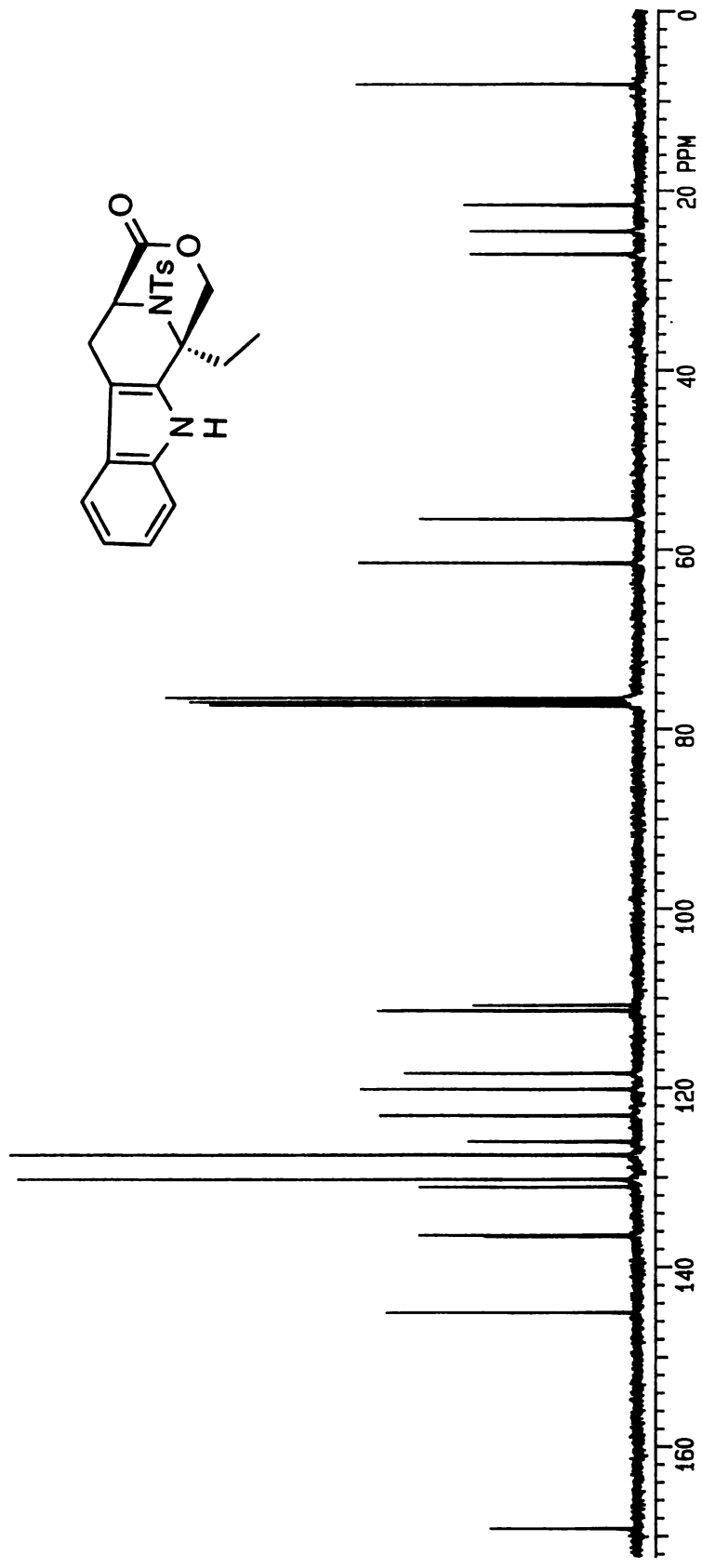


Figure 72 - ^{13}C NMR Spectrum of 92

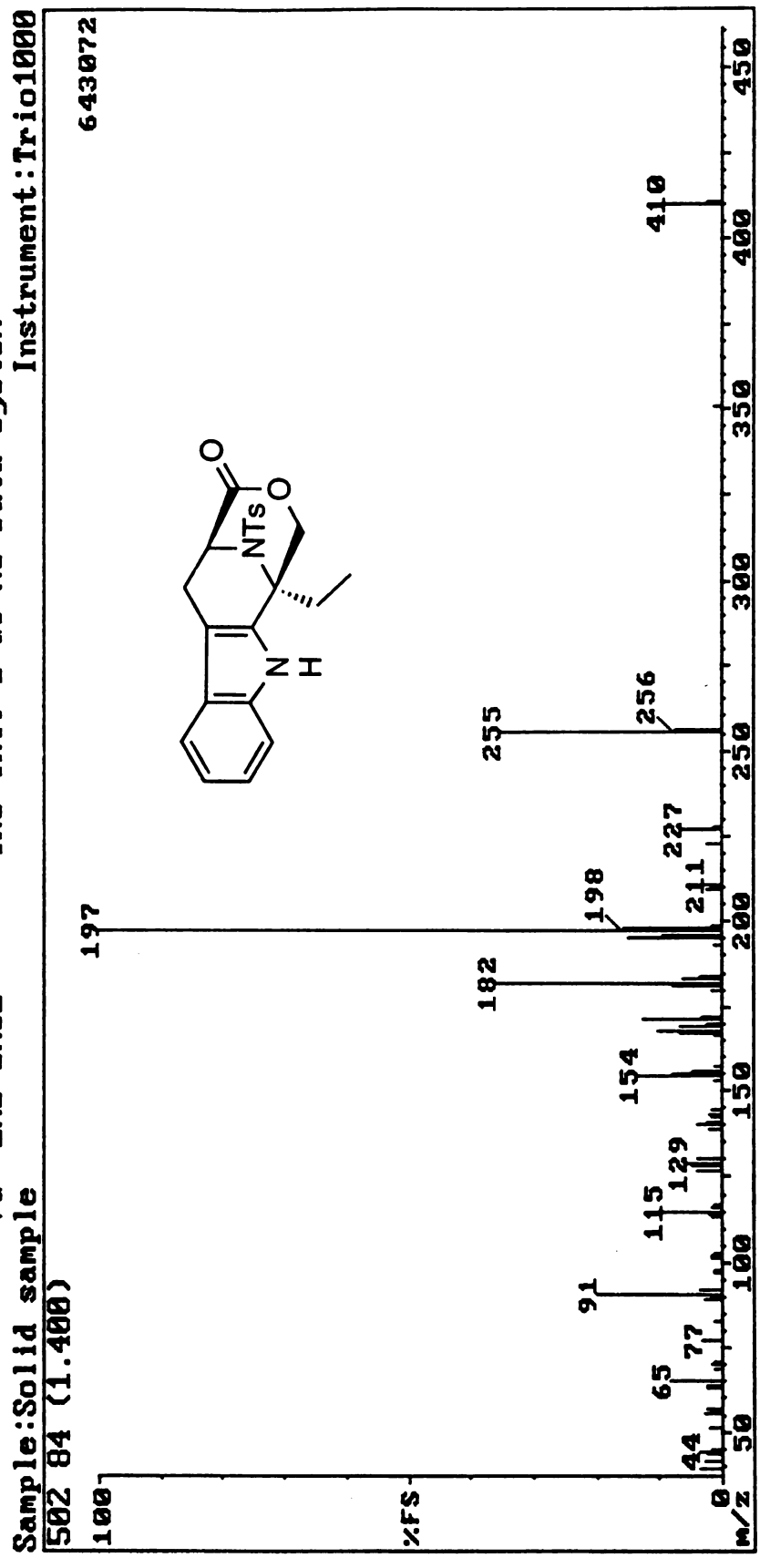


Figure 73 - Mass Spectrum of 92

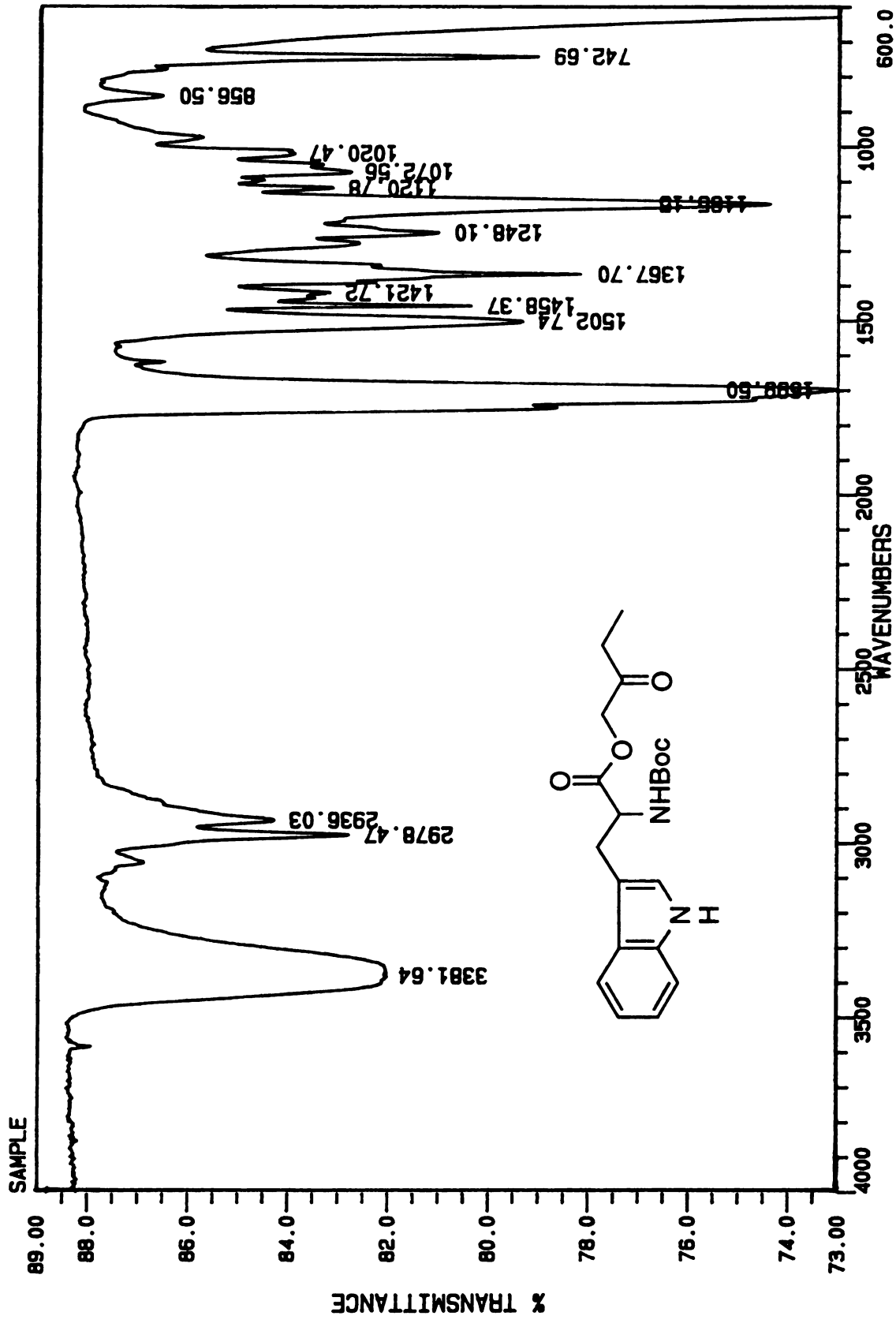


Figure 74 - IR Spectrum of 96

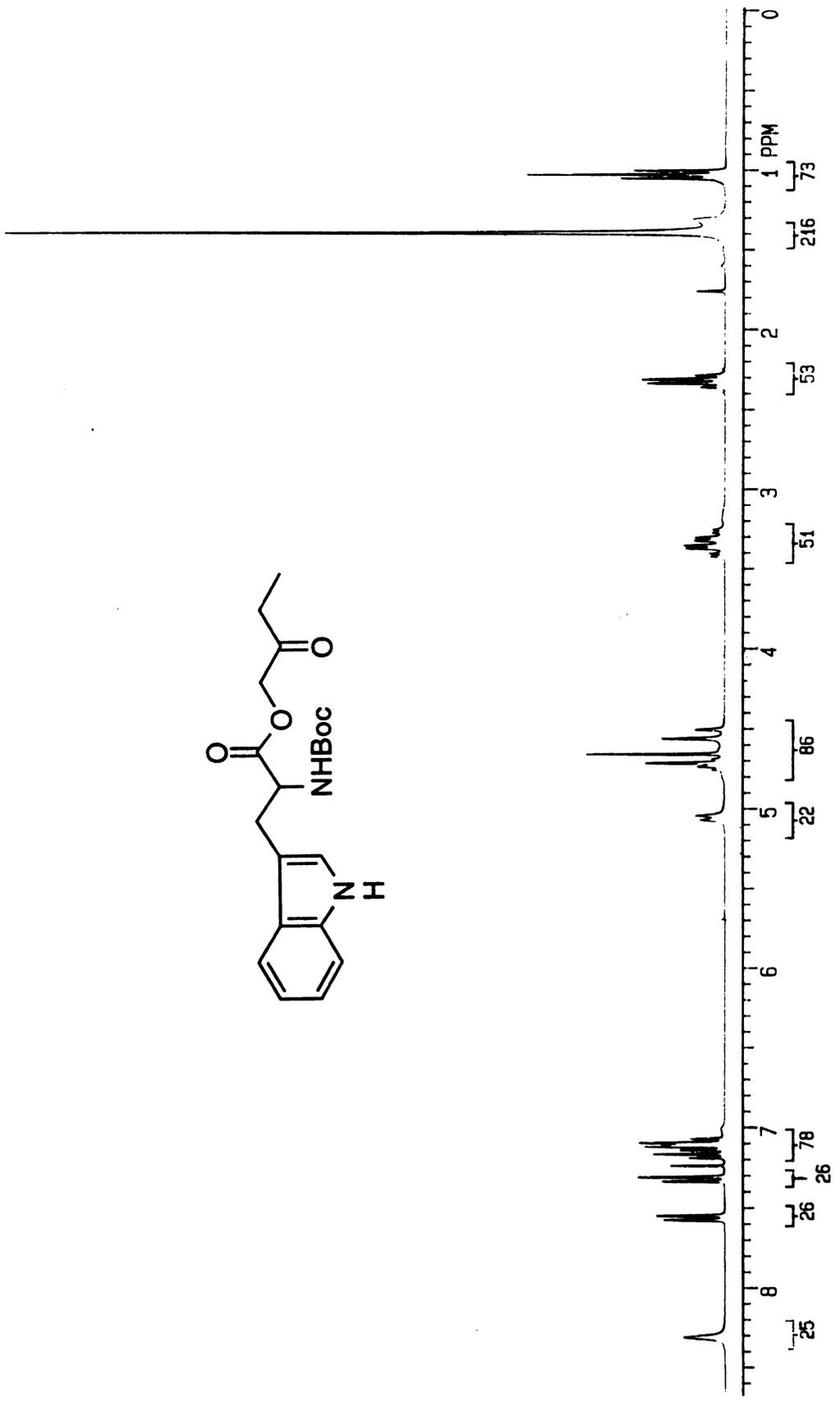


Figure 75 - ^{1}H NMR Spectrum of 96

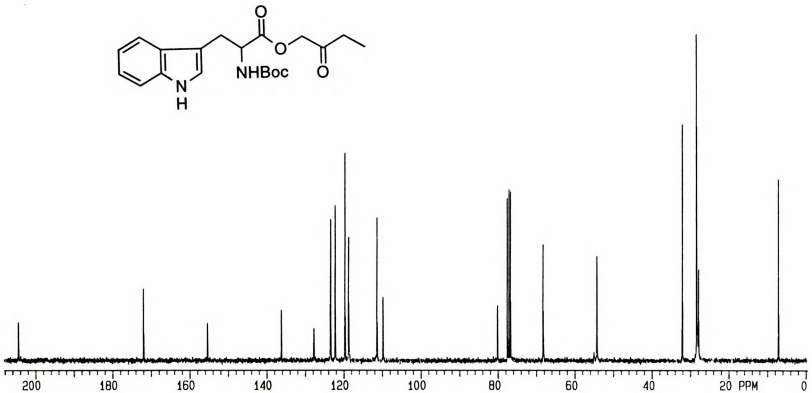


Figure 76 - ^{13}C NMR Spectrum of 96

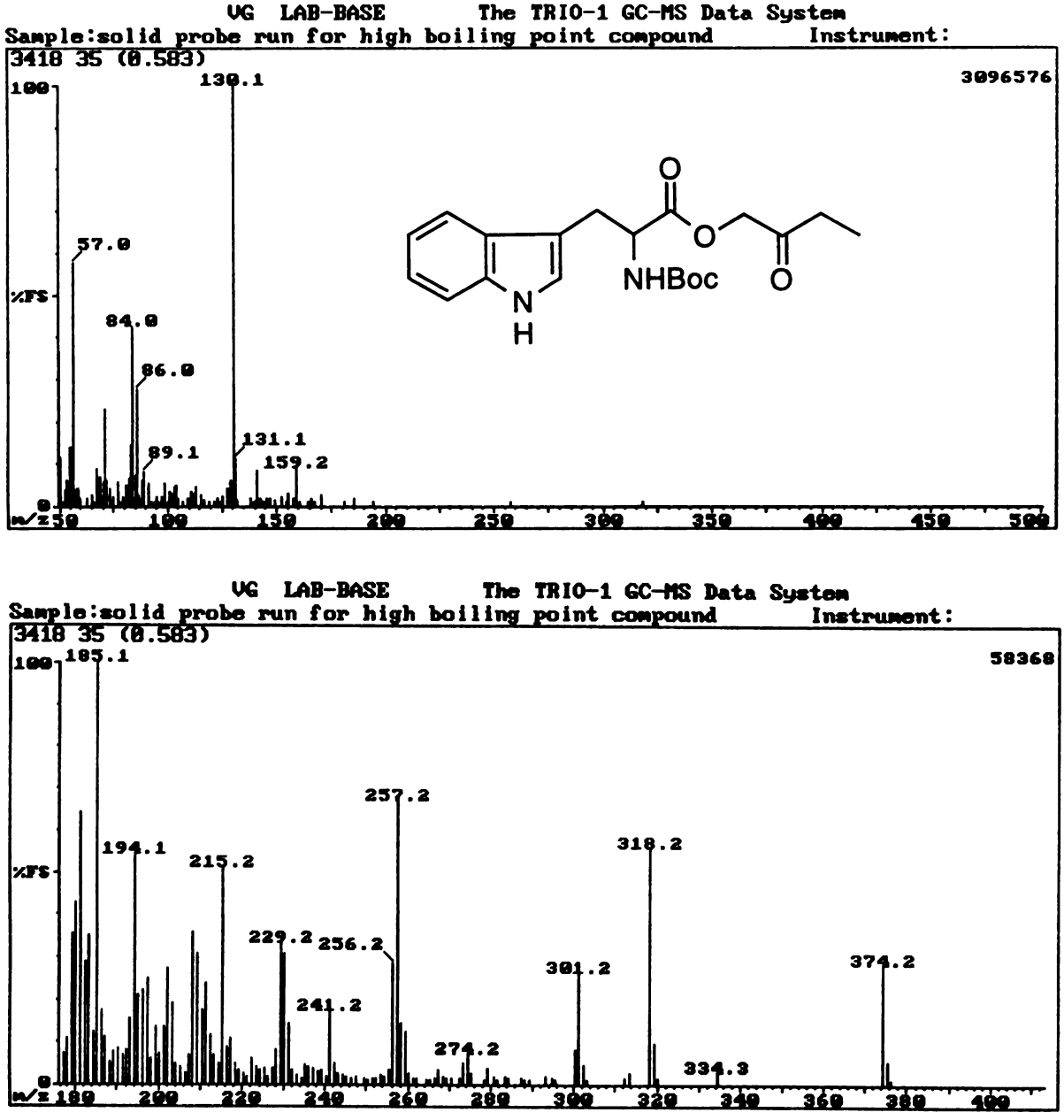


Figure 77 - Mass Spectrum of 96

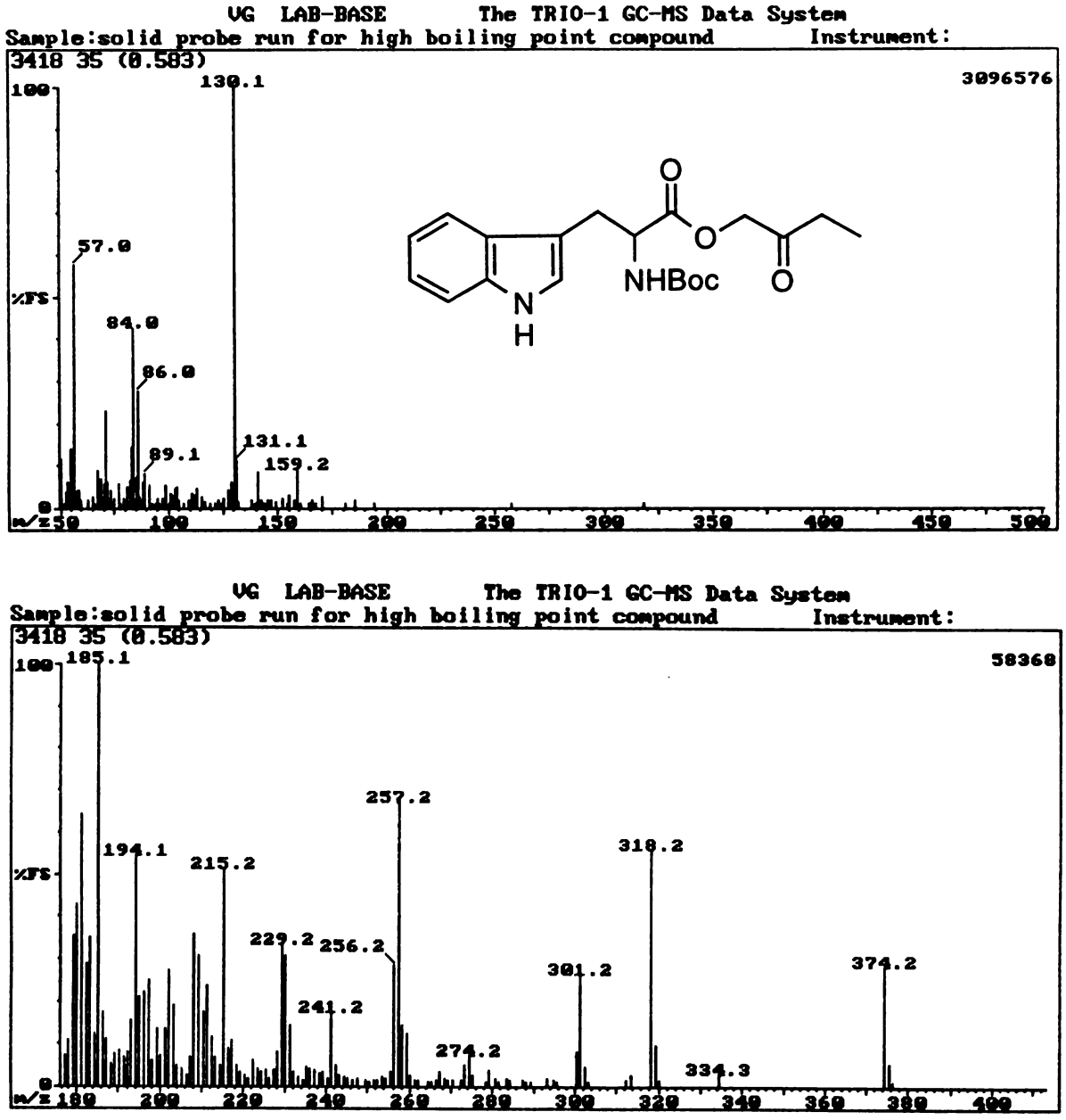


Figure 77 - Mass Spectrum of 96

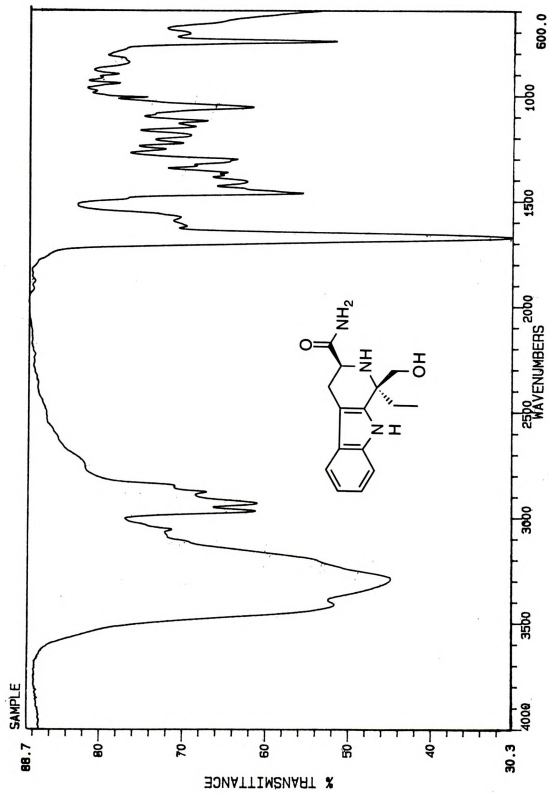


Figure 78 - IR Spectrum of 100

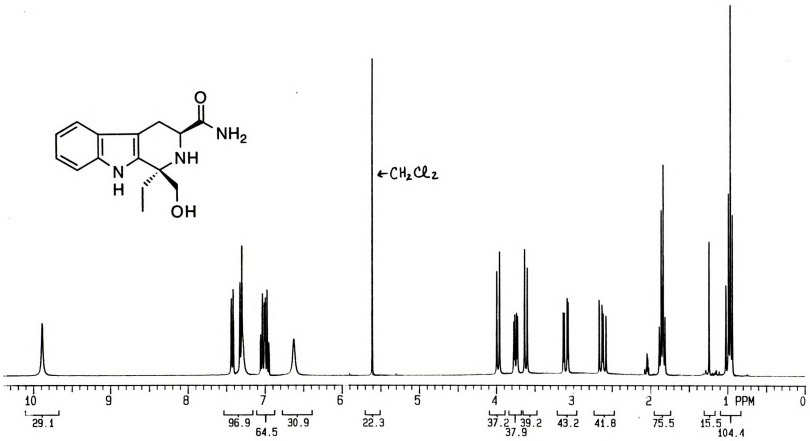


Figure 79 - ^{1}H NMR Spectrum of 100

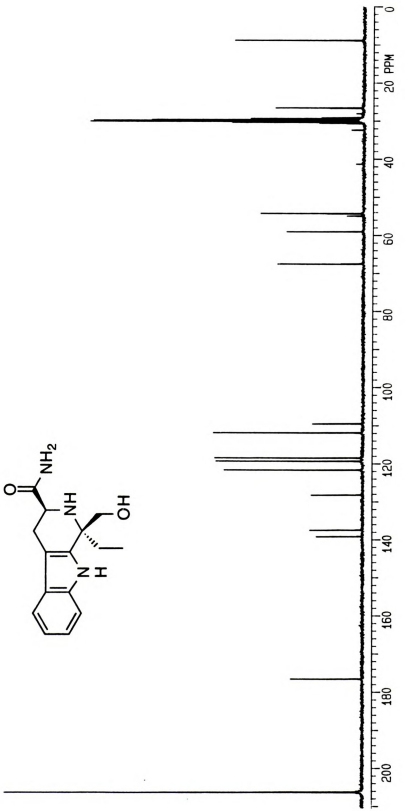


Figure 80 - ^{13}C NMR Spectrum of 100

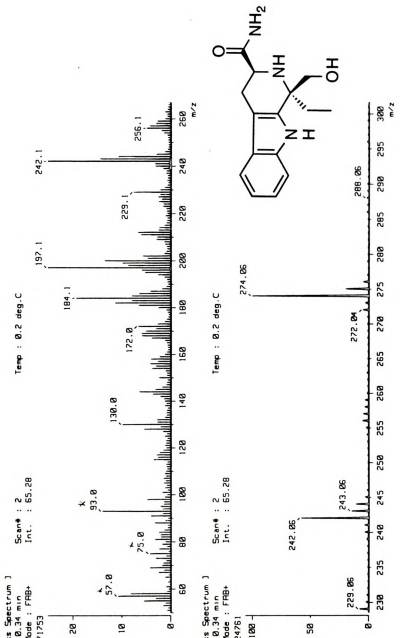


Figure 81 - Mass Spectrum of 100

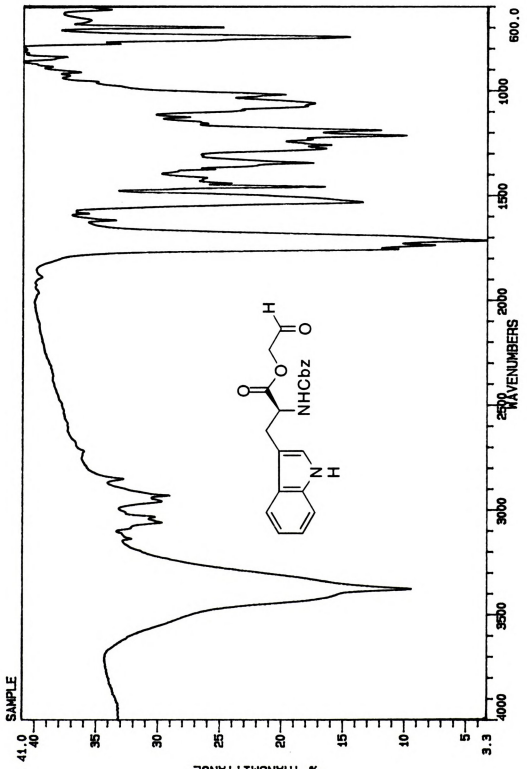


Figure 82 - IR Spectrum of 101

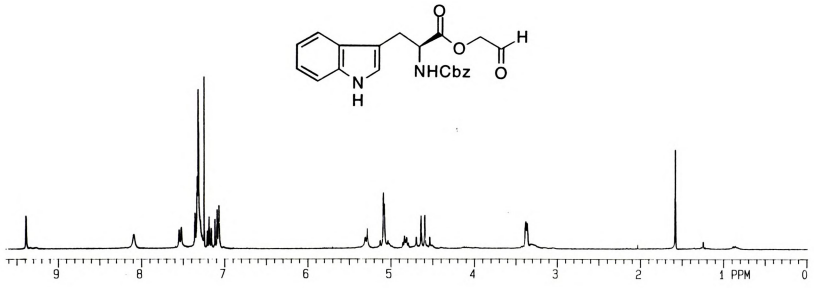


Figure 83 - ^{1}H NMR Spectrum of 101

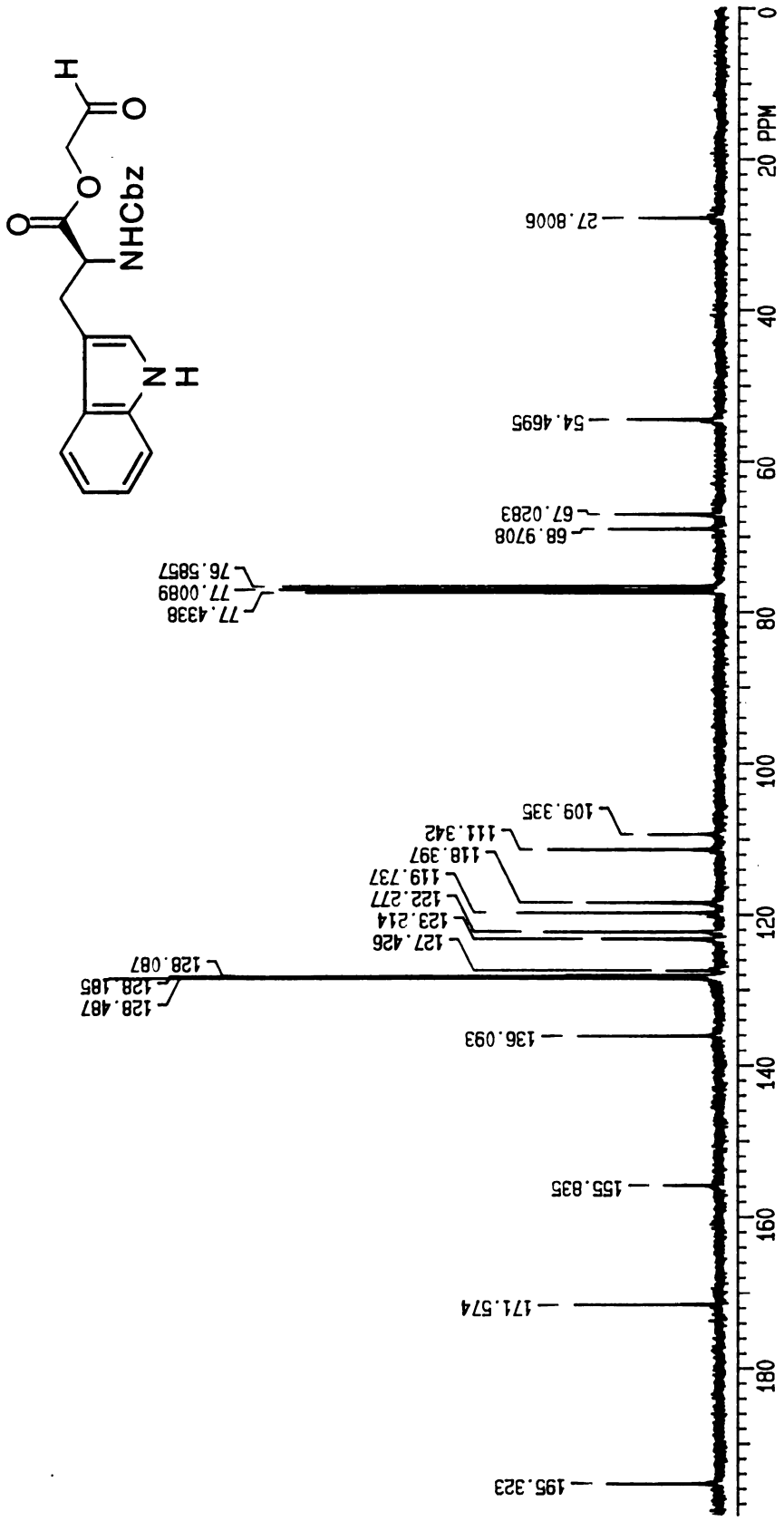


Figure 84 - ^{13}C NMR Spectrum of 101

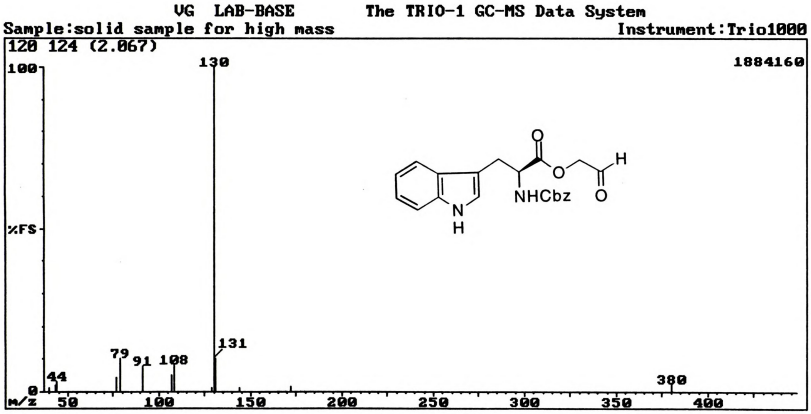


Figure 85 - Mass Spectrum of 101

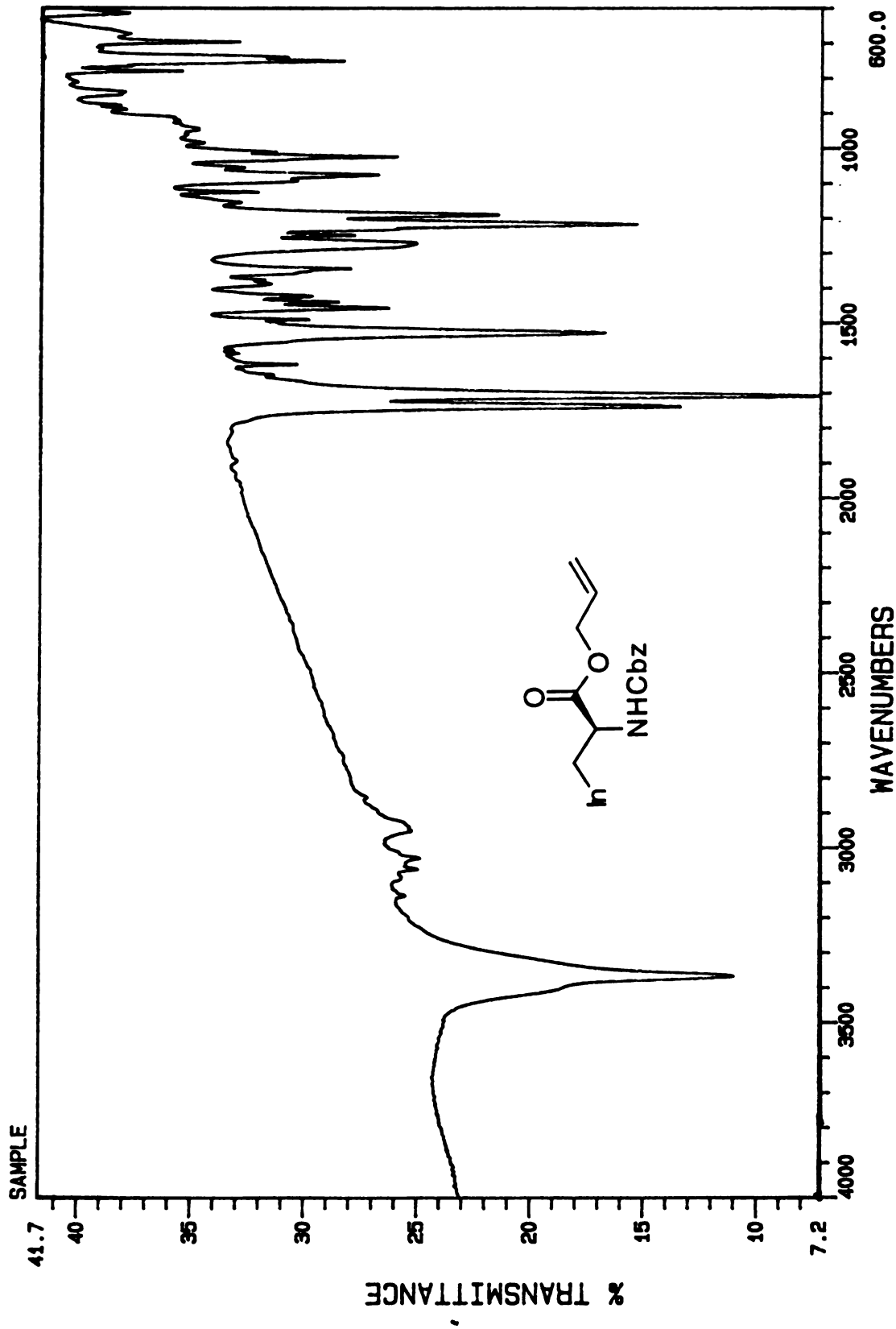


Figure 86 - IR Spectrum of 103

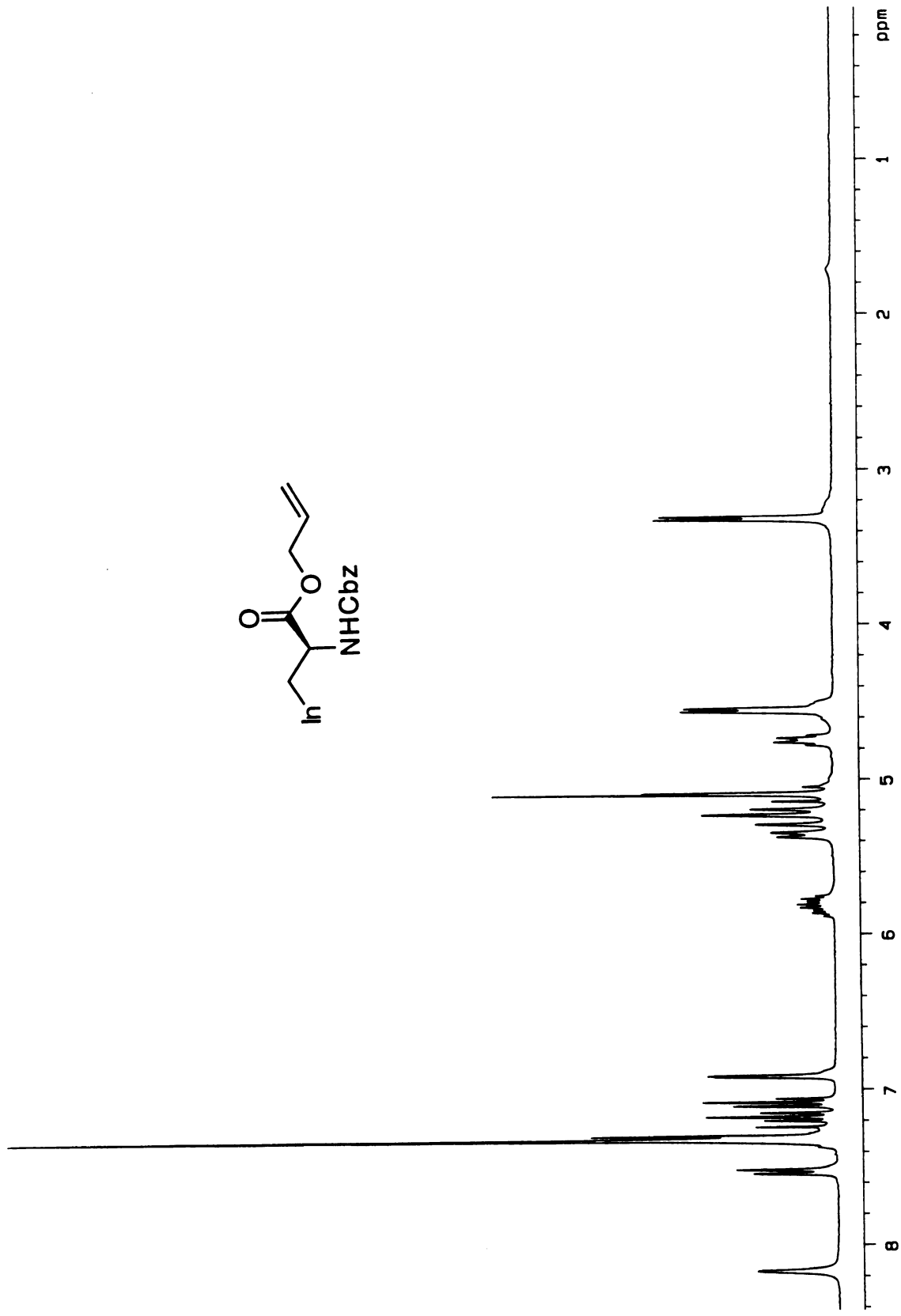


Figure 87 - ^{1}H NMR Spectrum of 103

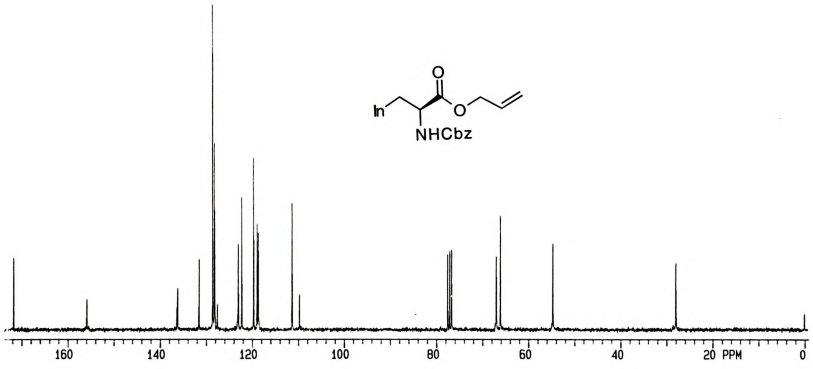


Figure 88 - ^{13}C NMR Spectrum of 103

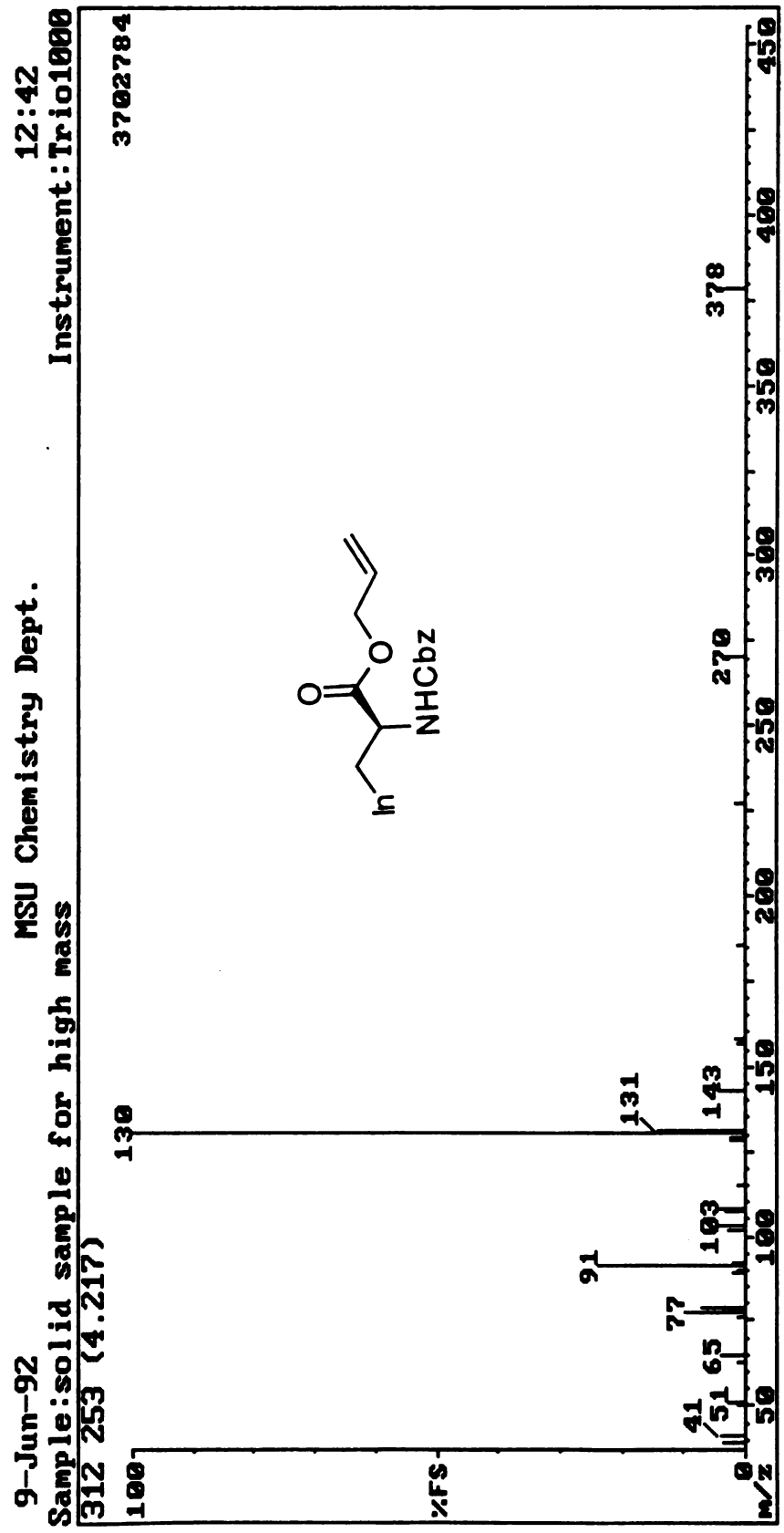


Figure 89 - Mass Spectrum of 103

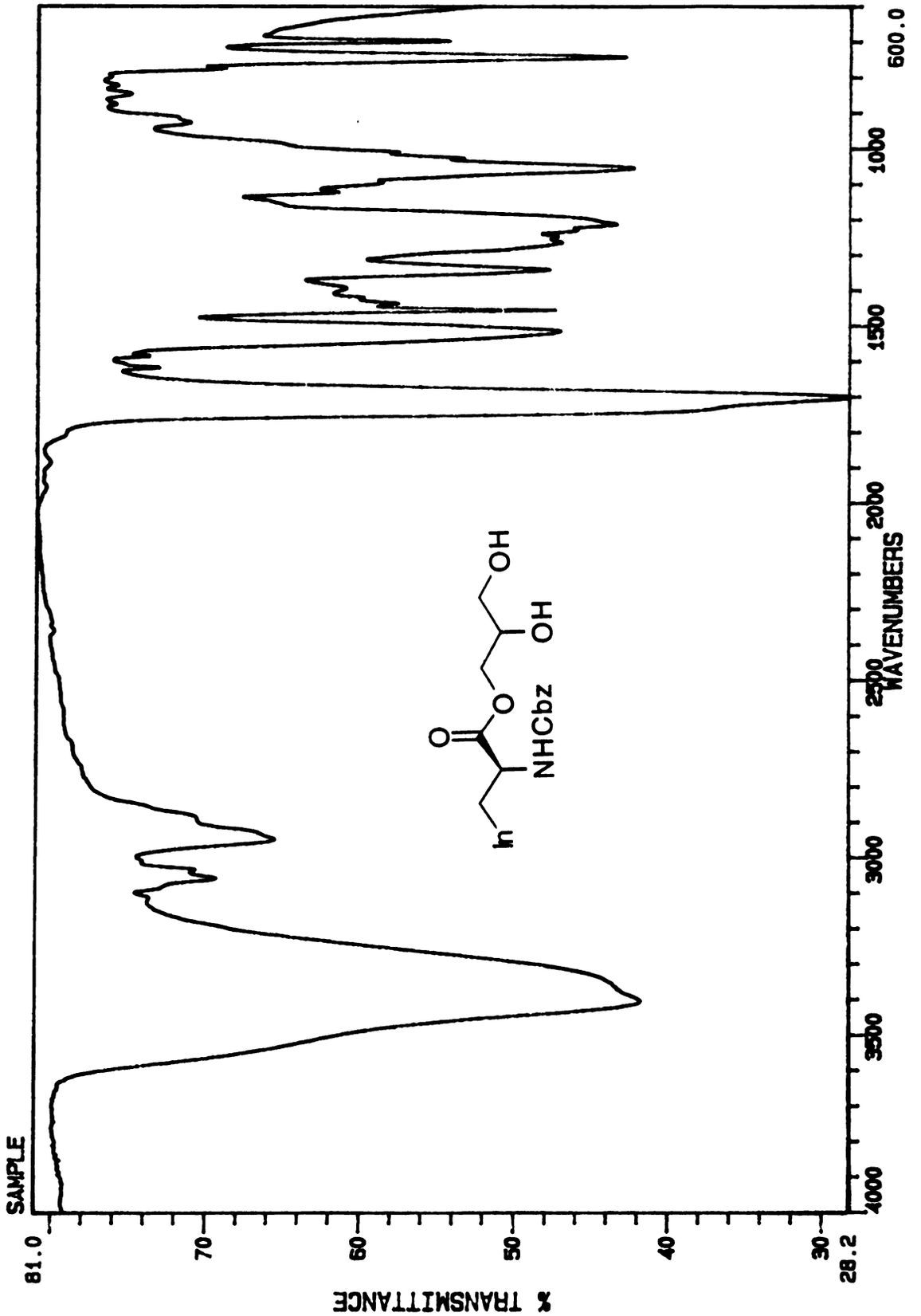


Figure 90 - IR Spectrum of 104

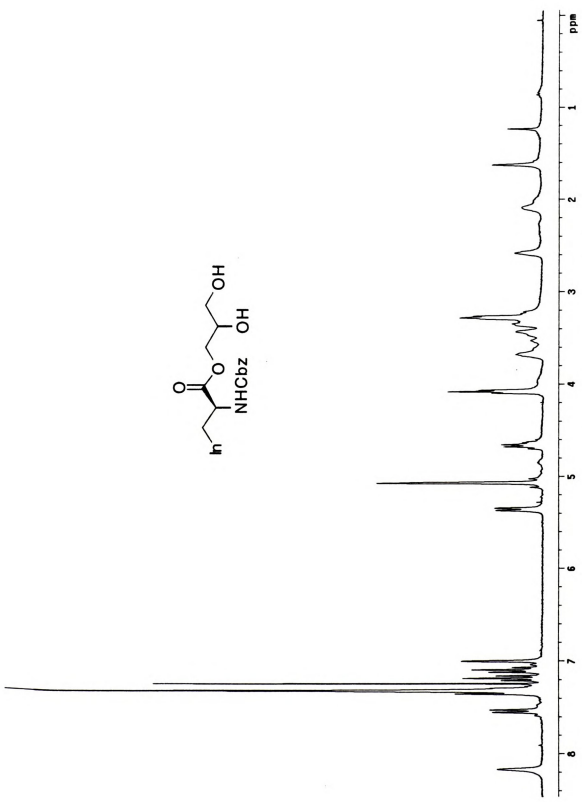


Figure 91 - ^{1}H NMR Spectrum of 104

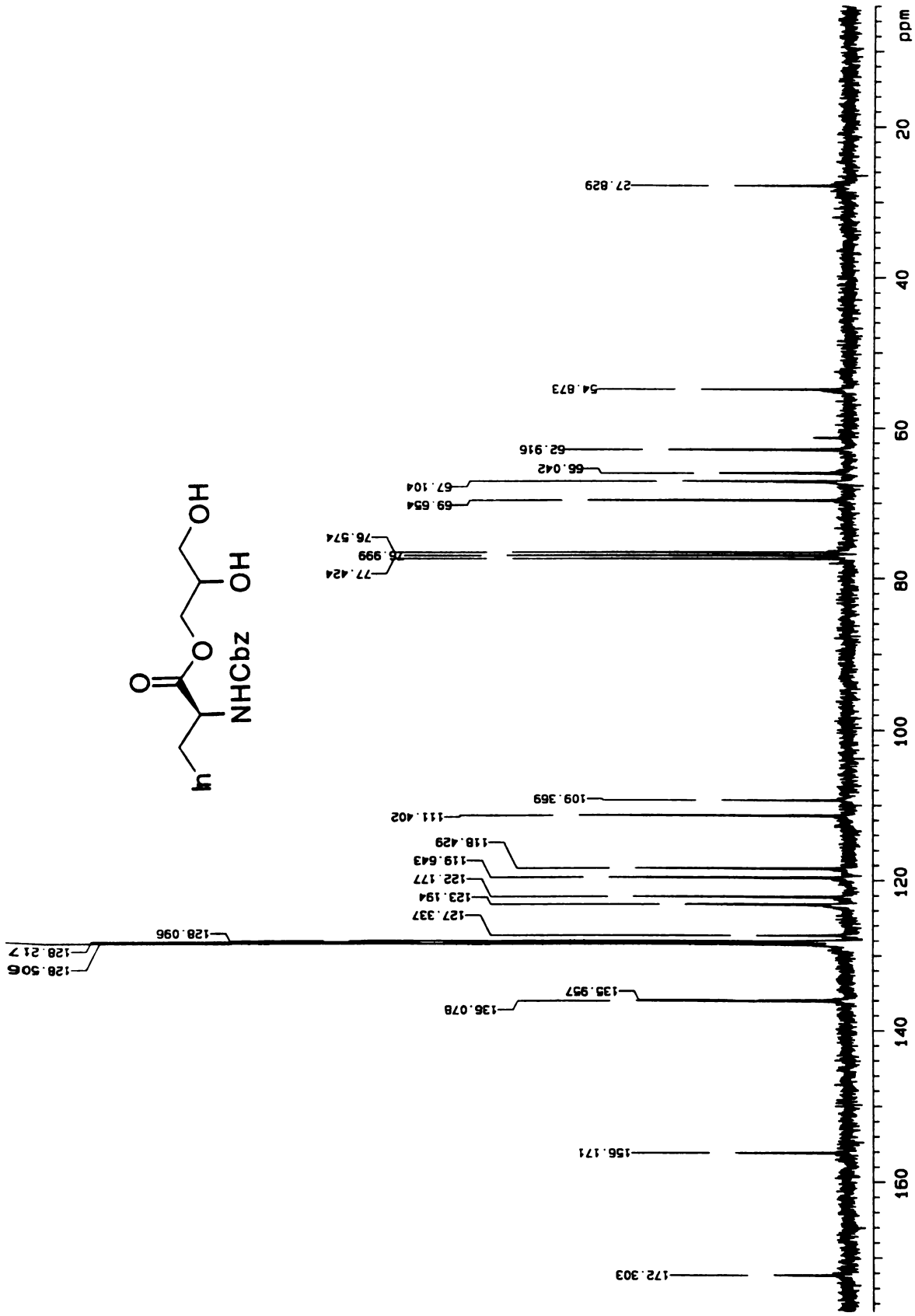


Figure 92 - ^{13}C NMR Spectrum of 104

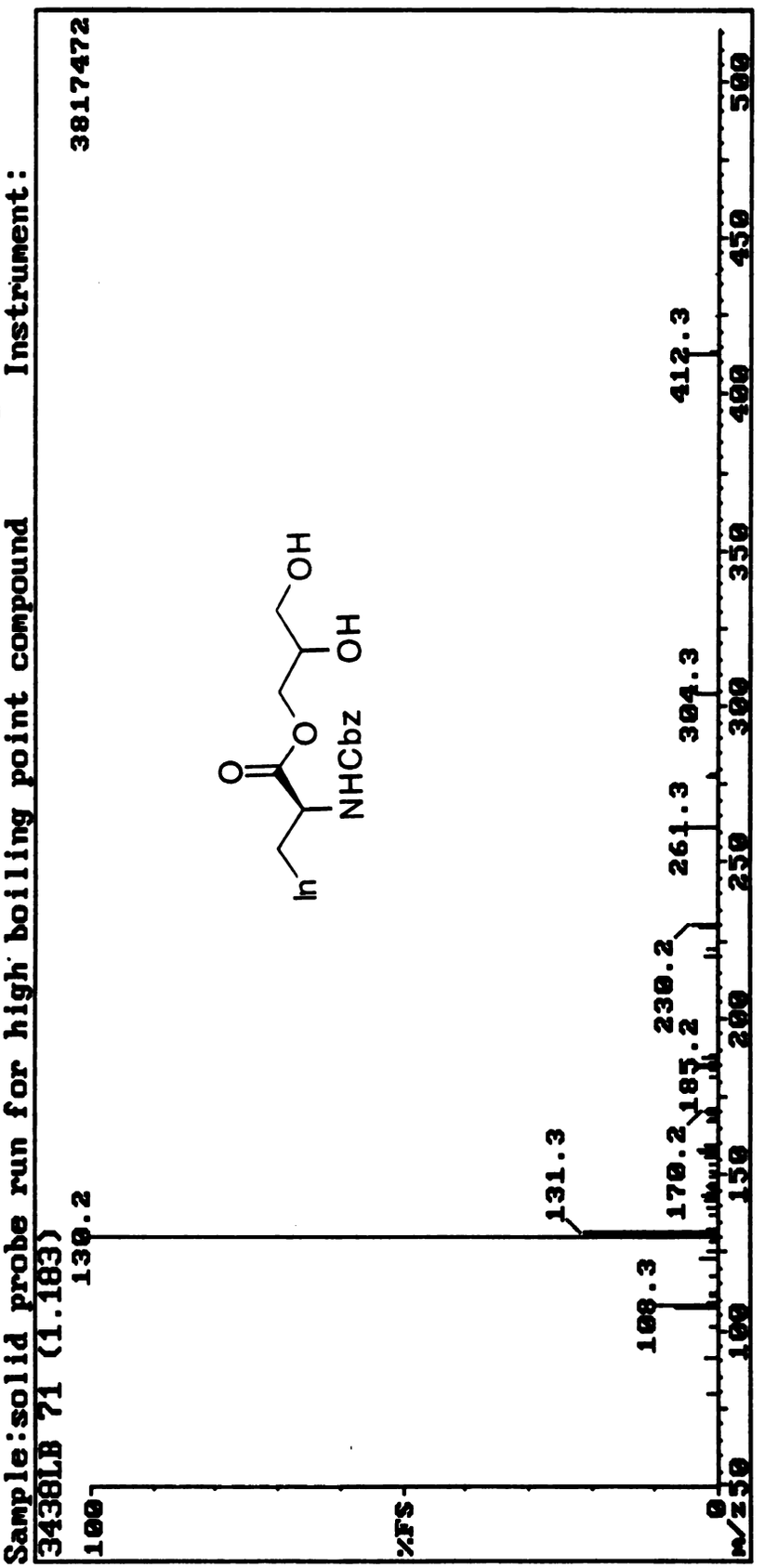


Figure 93 - Mass Spectrum of 104

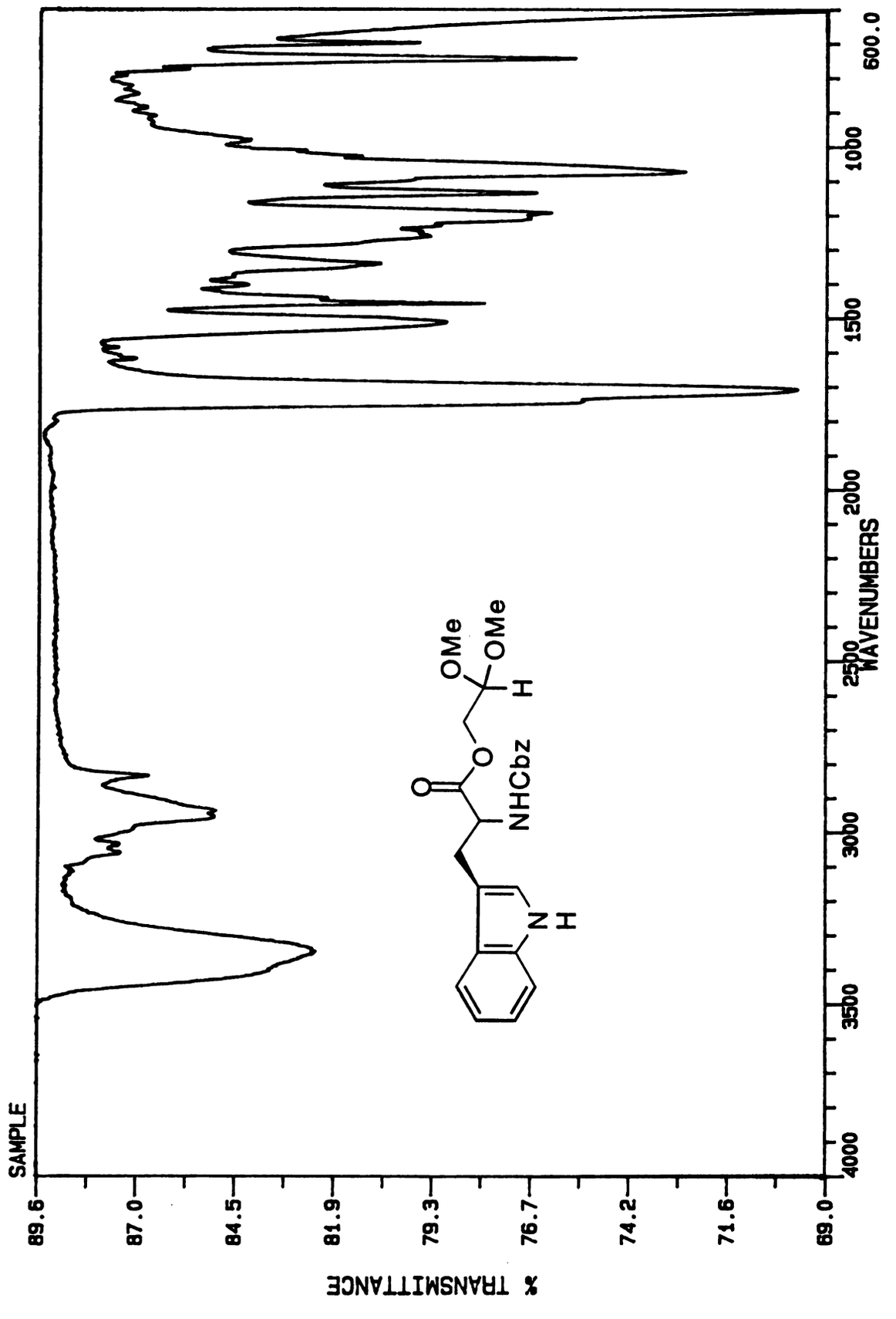


Figure 94 - IR Spectrum of 109

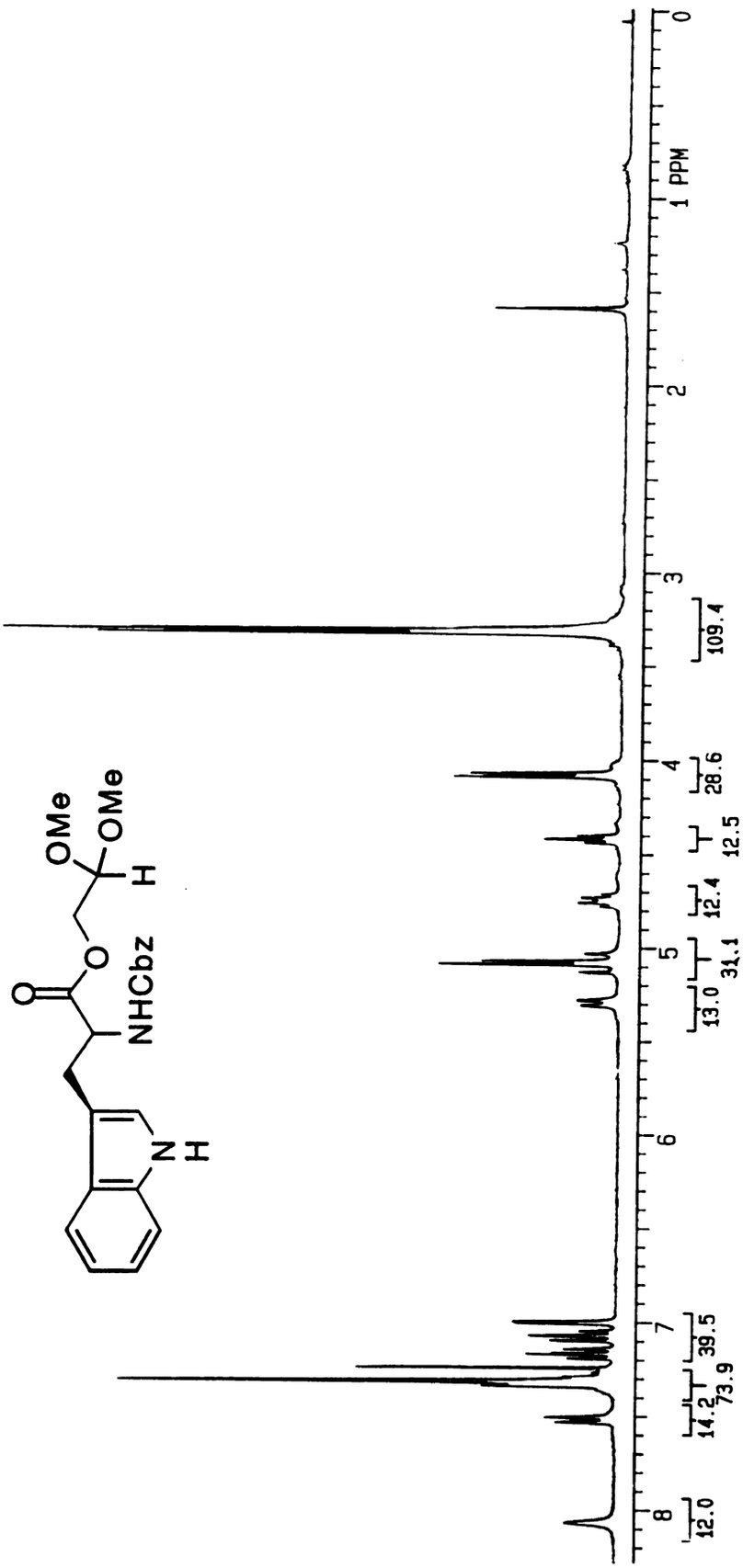


Figure 95 - ^{1}H NMR Spectrum of 109

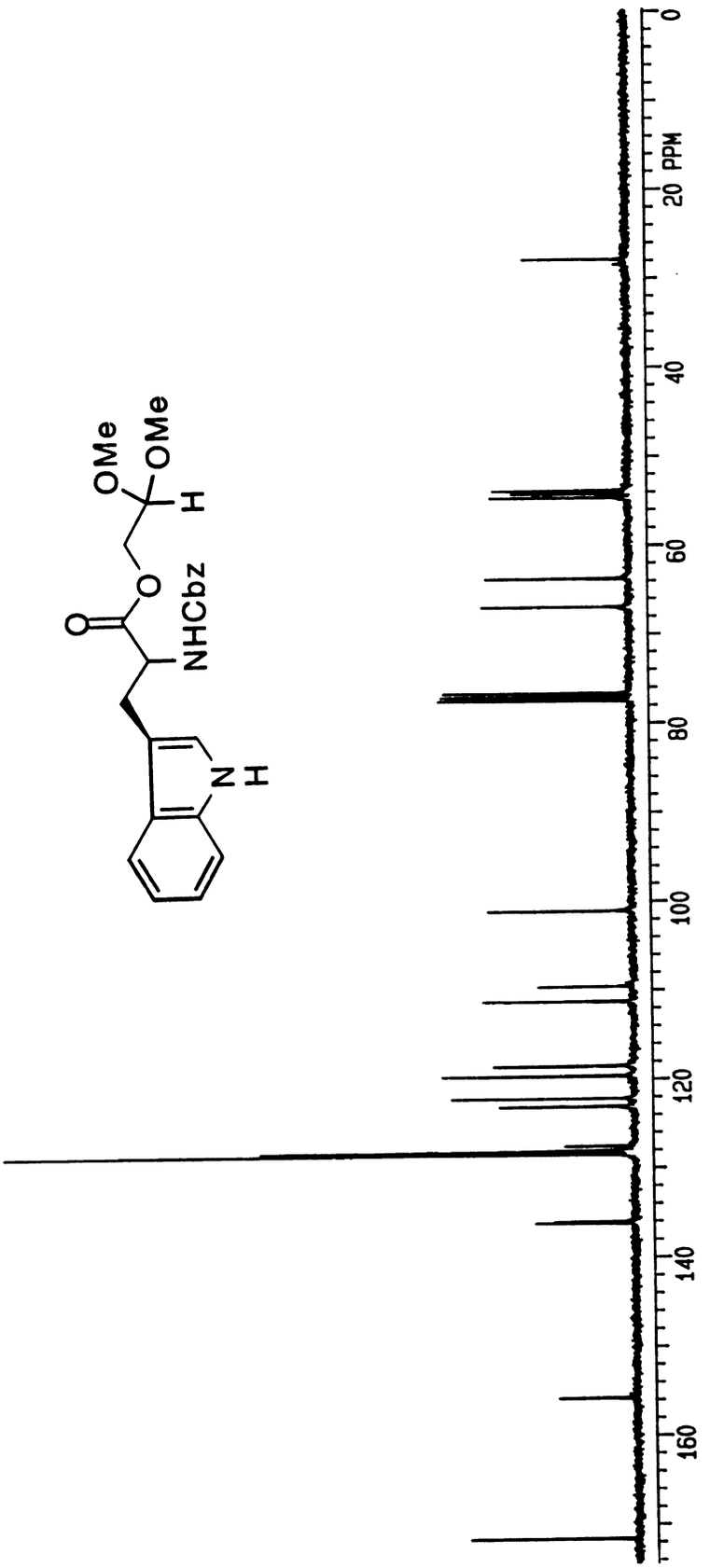
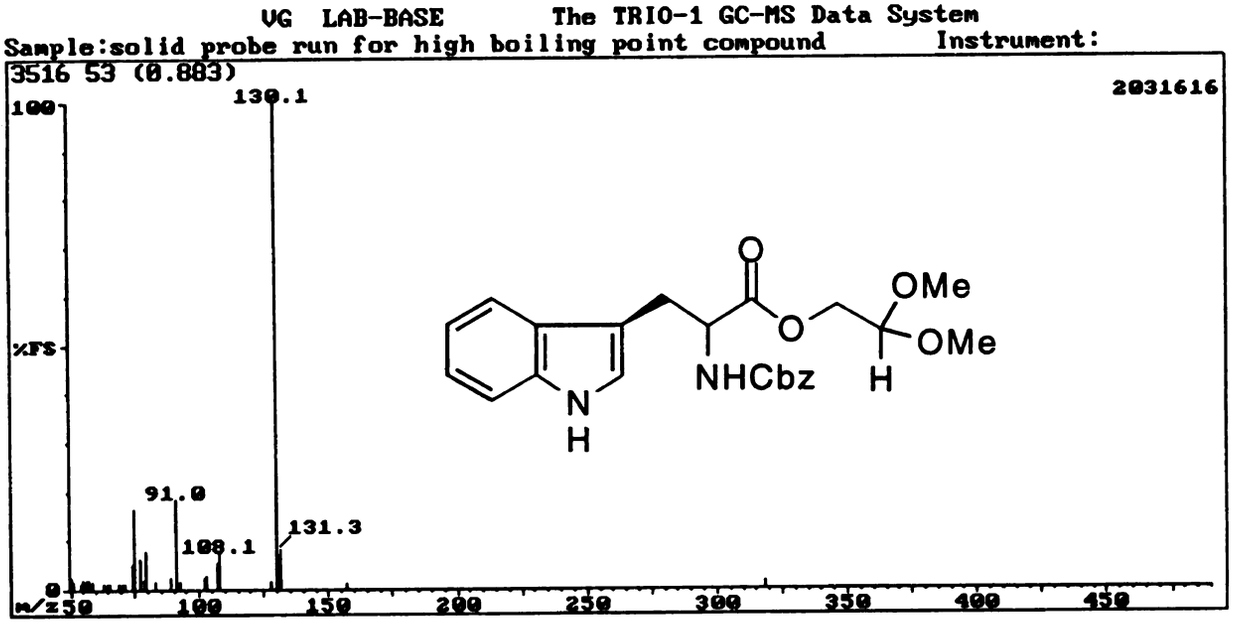


Figure 96 - ^{13}C NMR Spectrum of 109



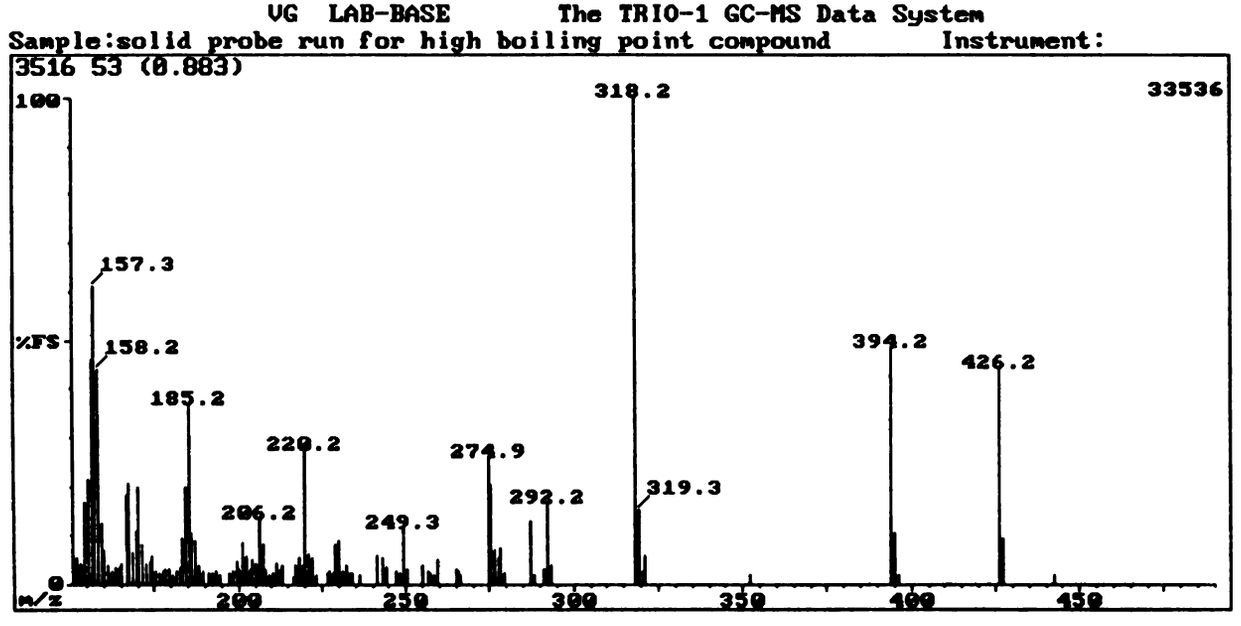


Figure 97 - Mass Spectrum of 109

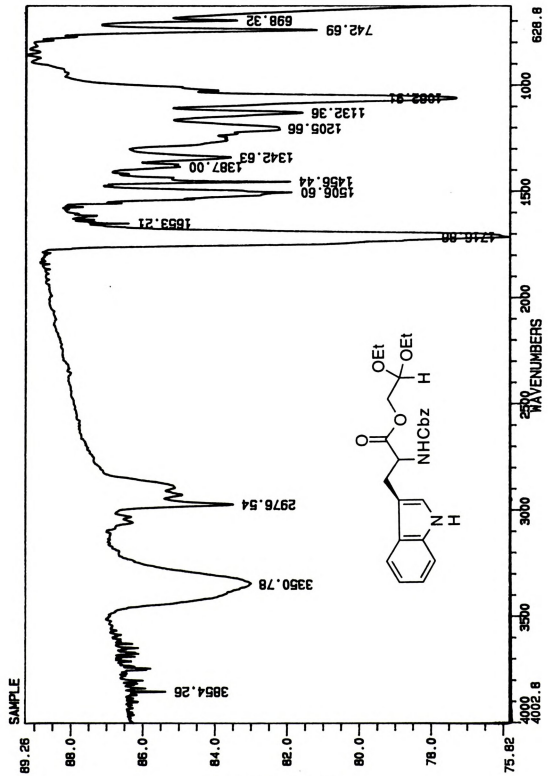


Figure 98 - IR Spectrum of 110

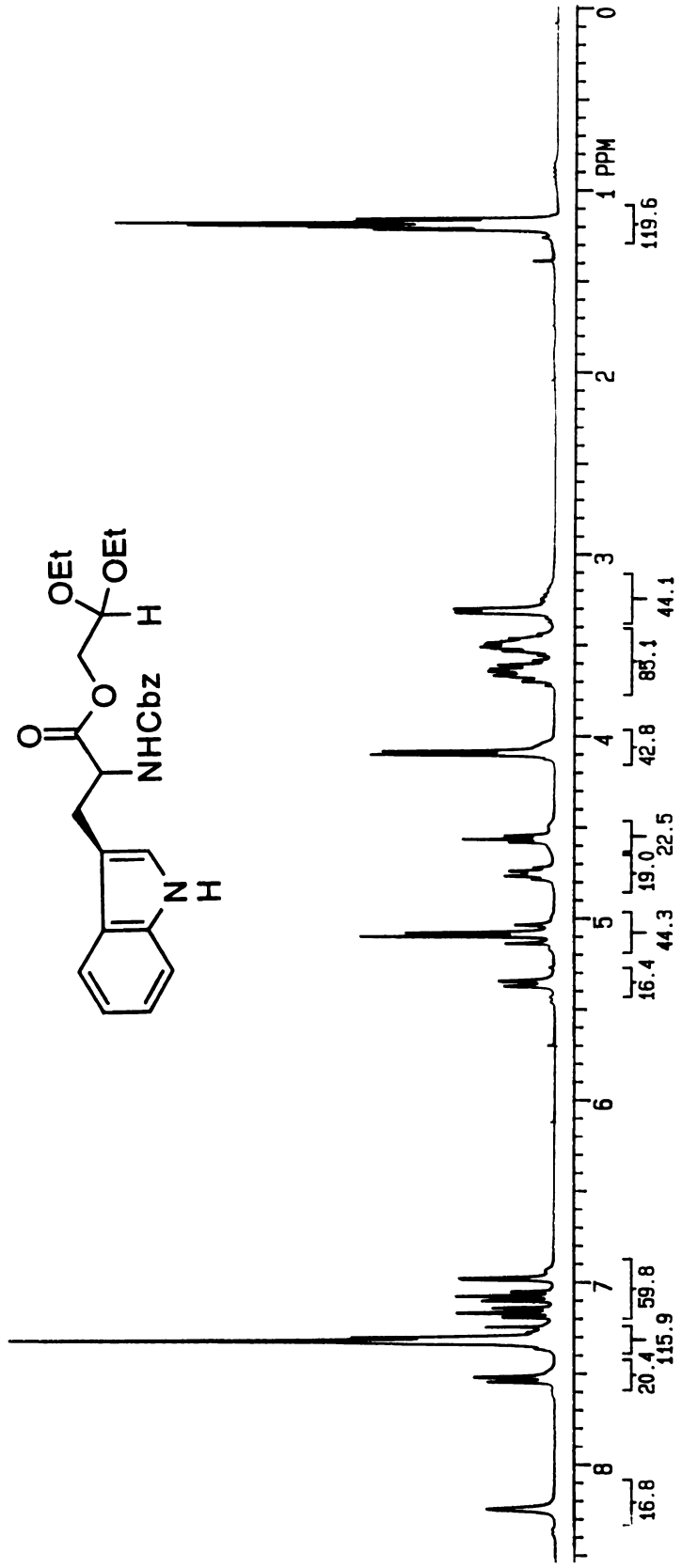


Figure 99 - ^{1}H NMR Spectrum of 110

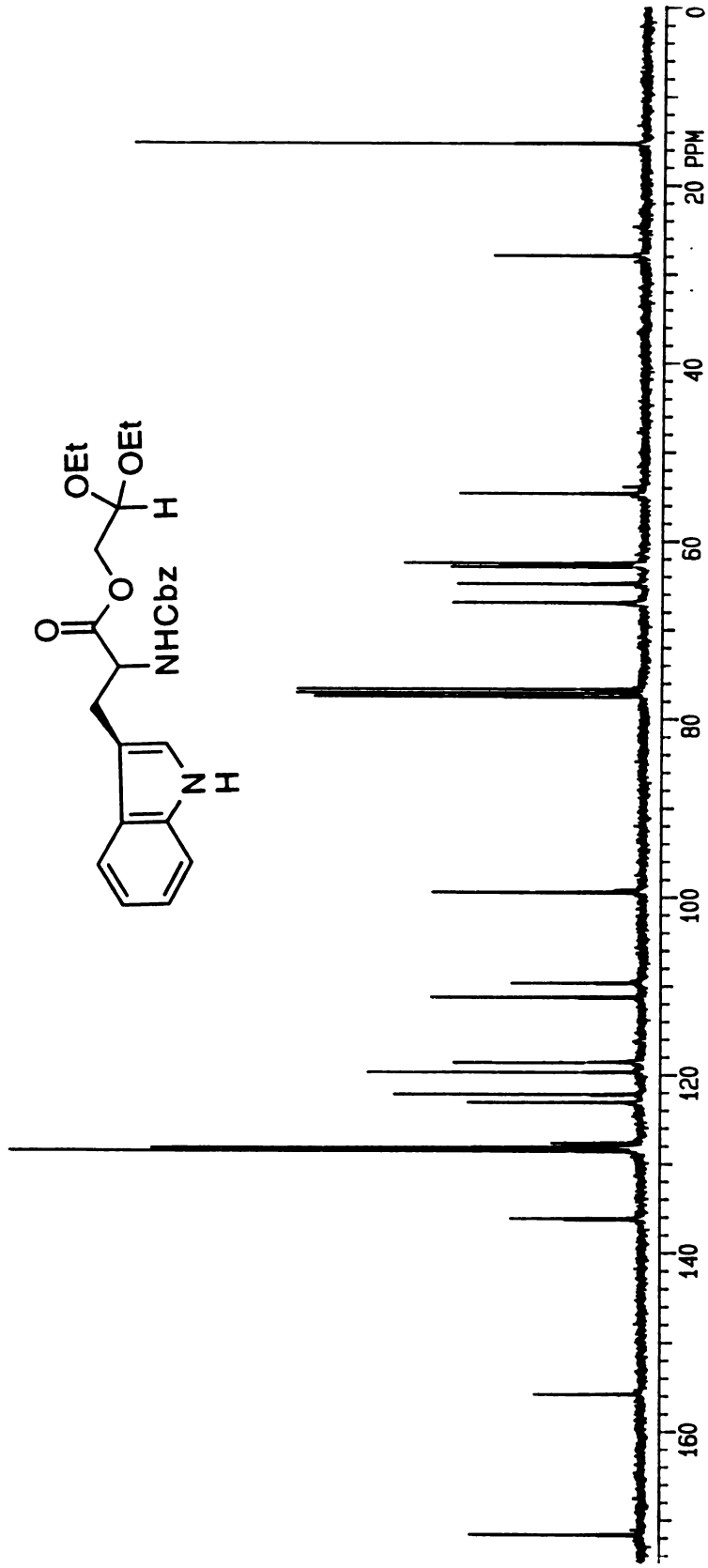


Figure 100 - ^{13}C NMR Spectrum of 110

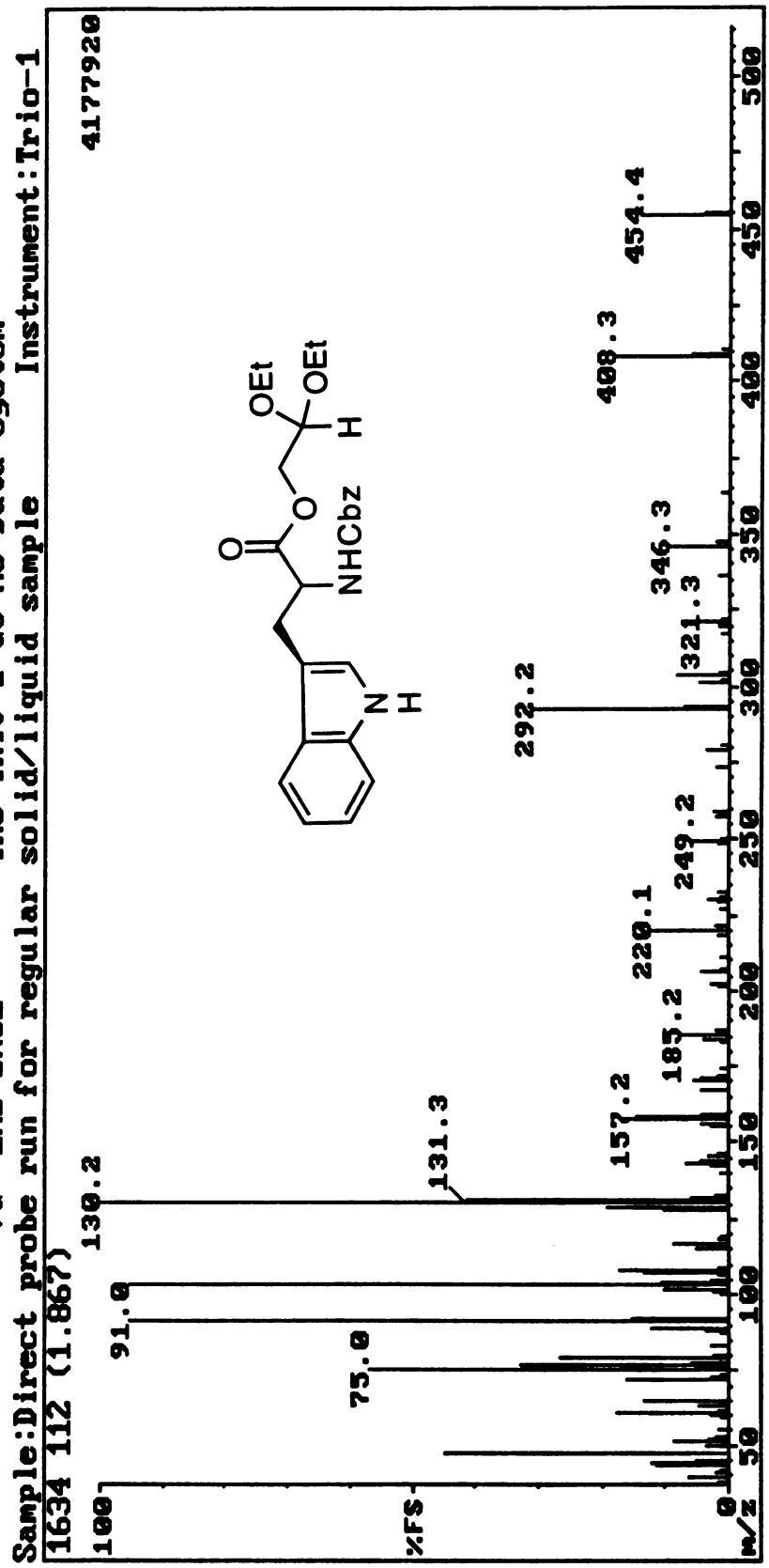


Figure 101 - Mass Spectrum of 110

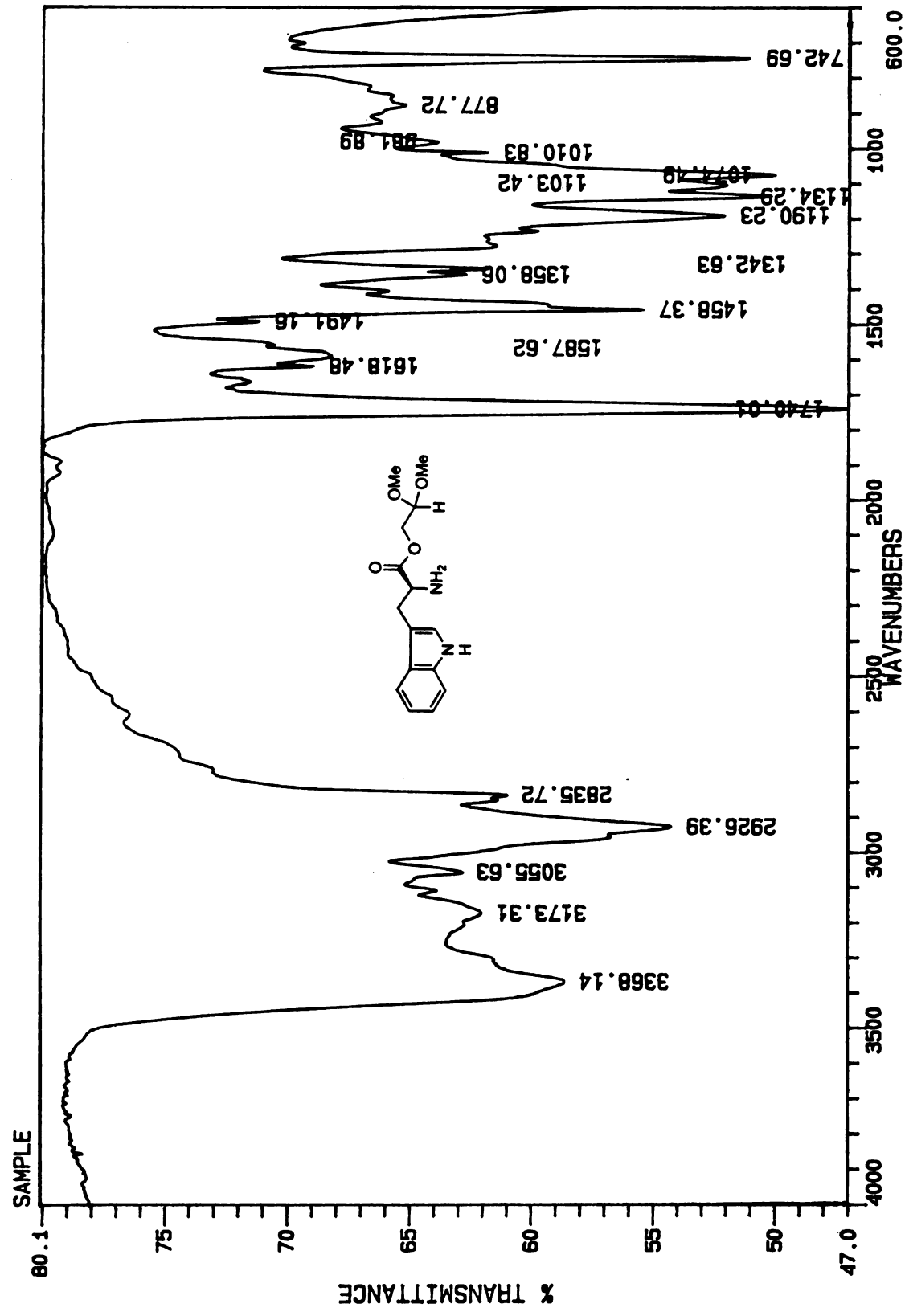


Figure 102 - IR Spectrum of 111

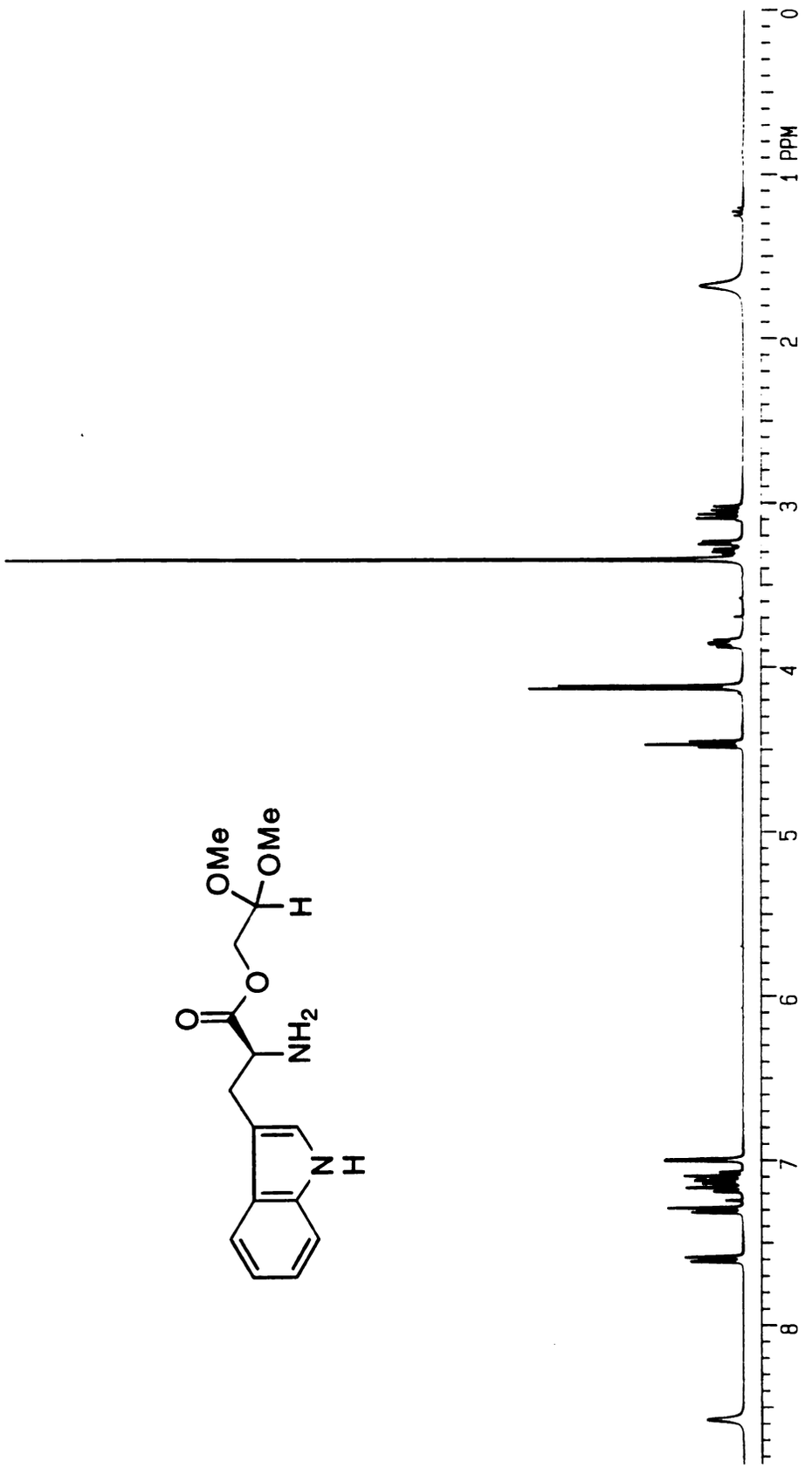


Figure 103 - ^{1}H NMR Spectrum of 111

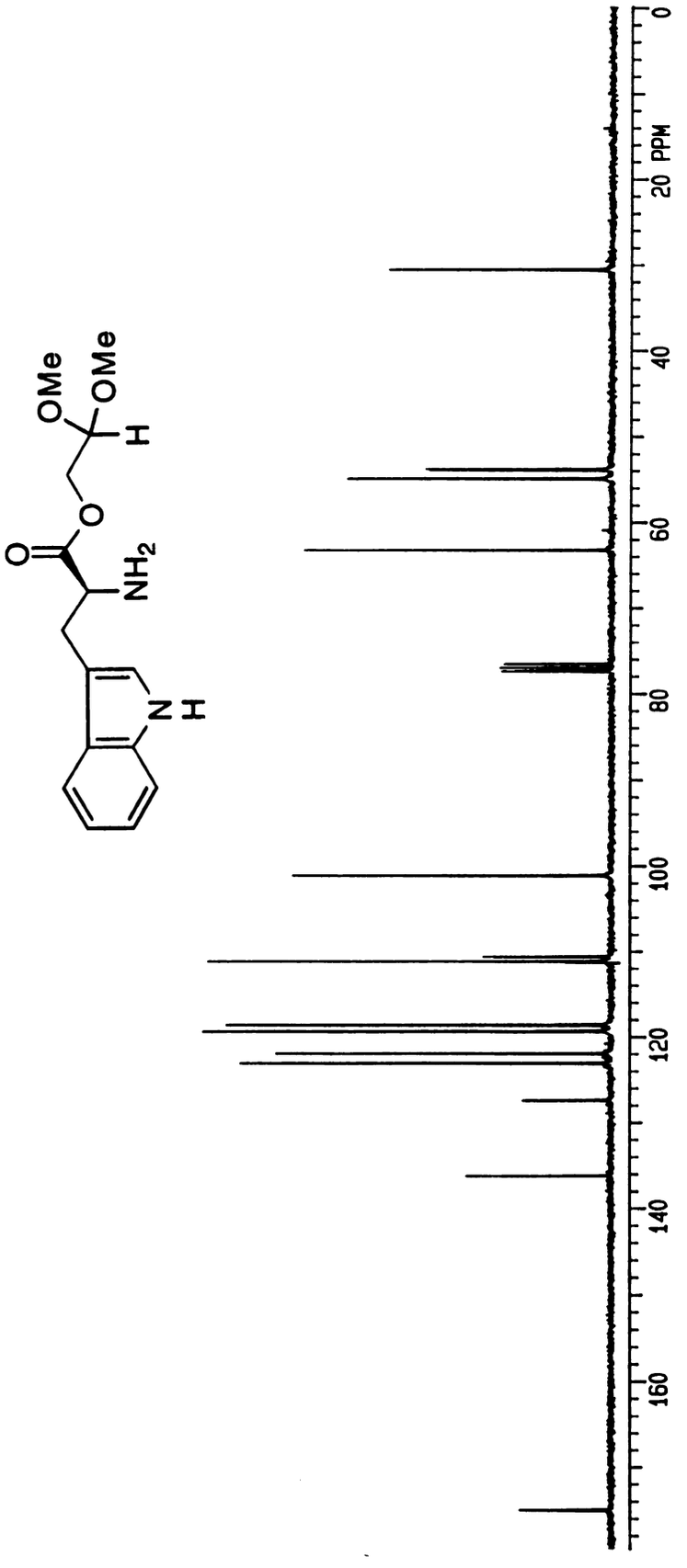


Figure 104 - ^{13}C NMR Spectrum of 111

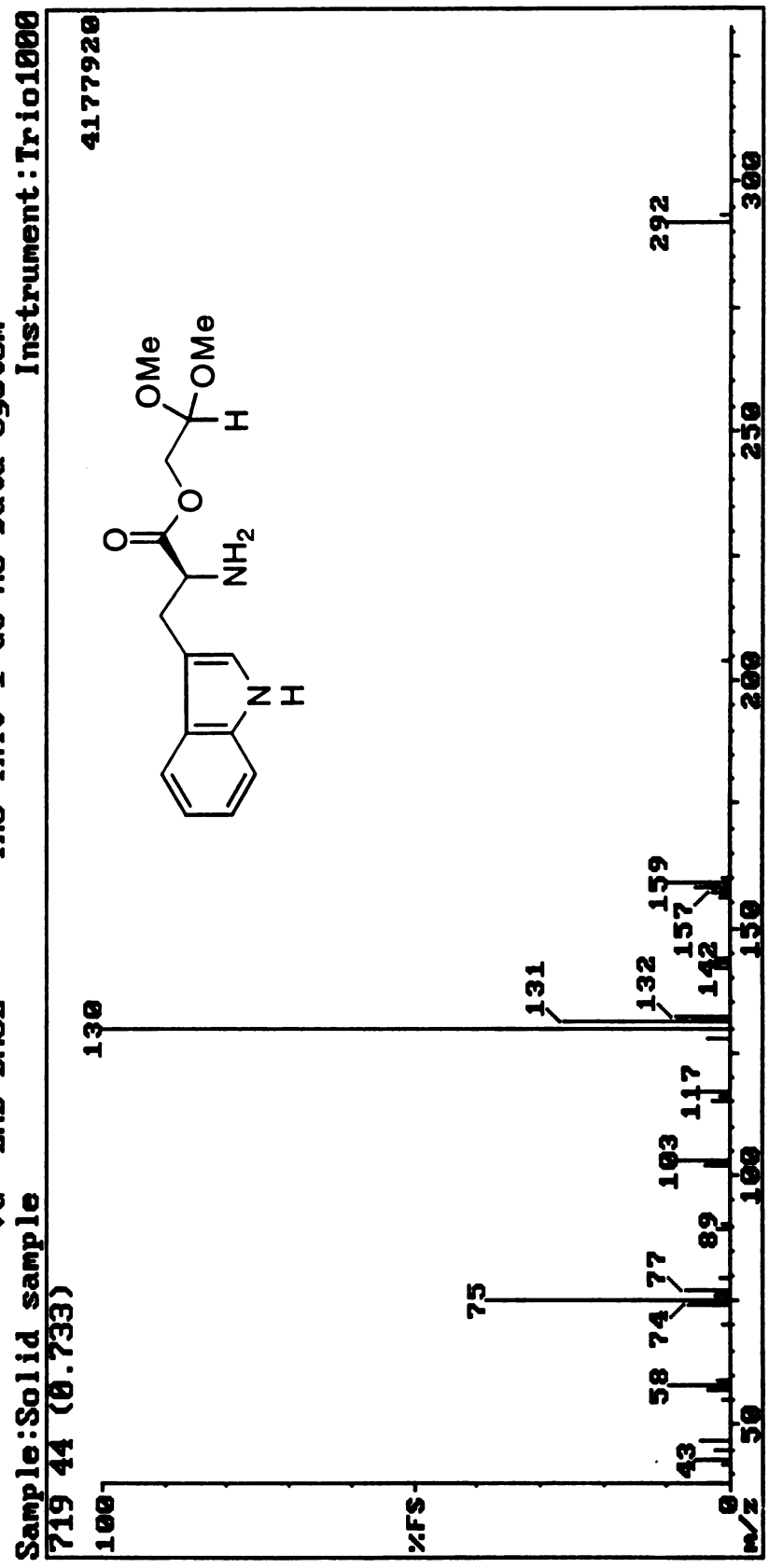


Figure 105 - Mass Spectrum of 111

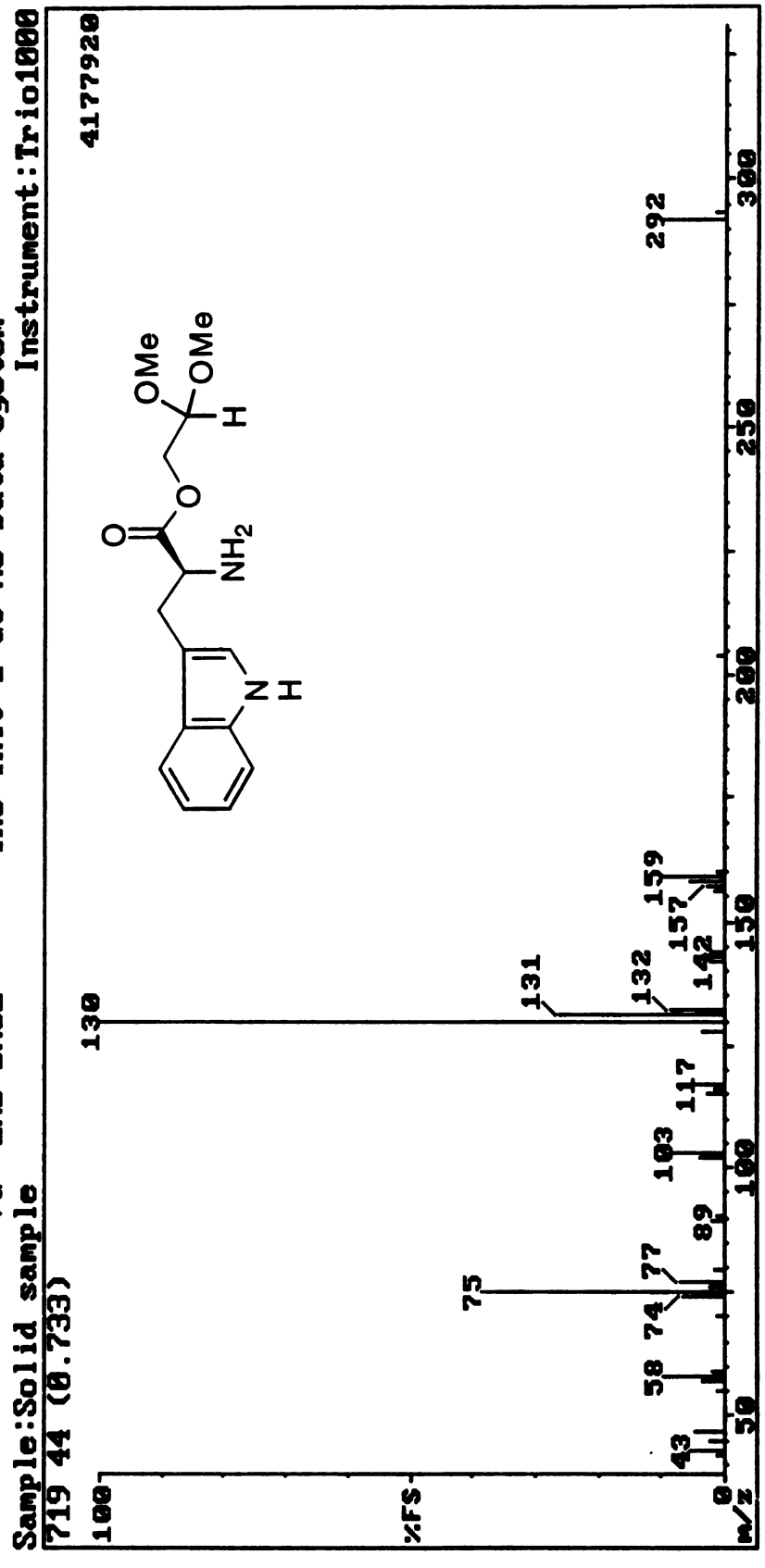


Figure 105 - Mass Spectrum of 111

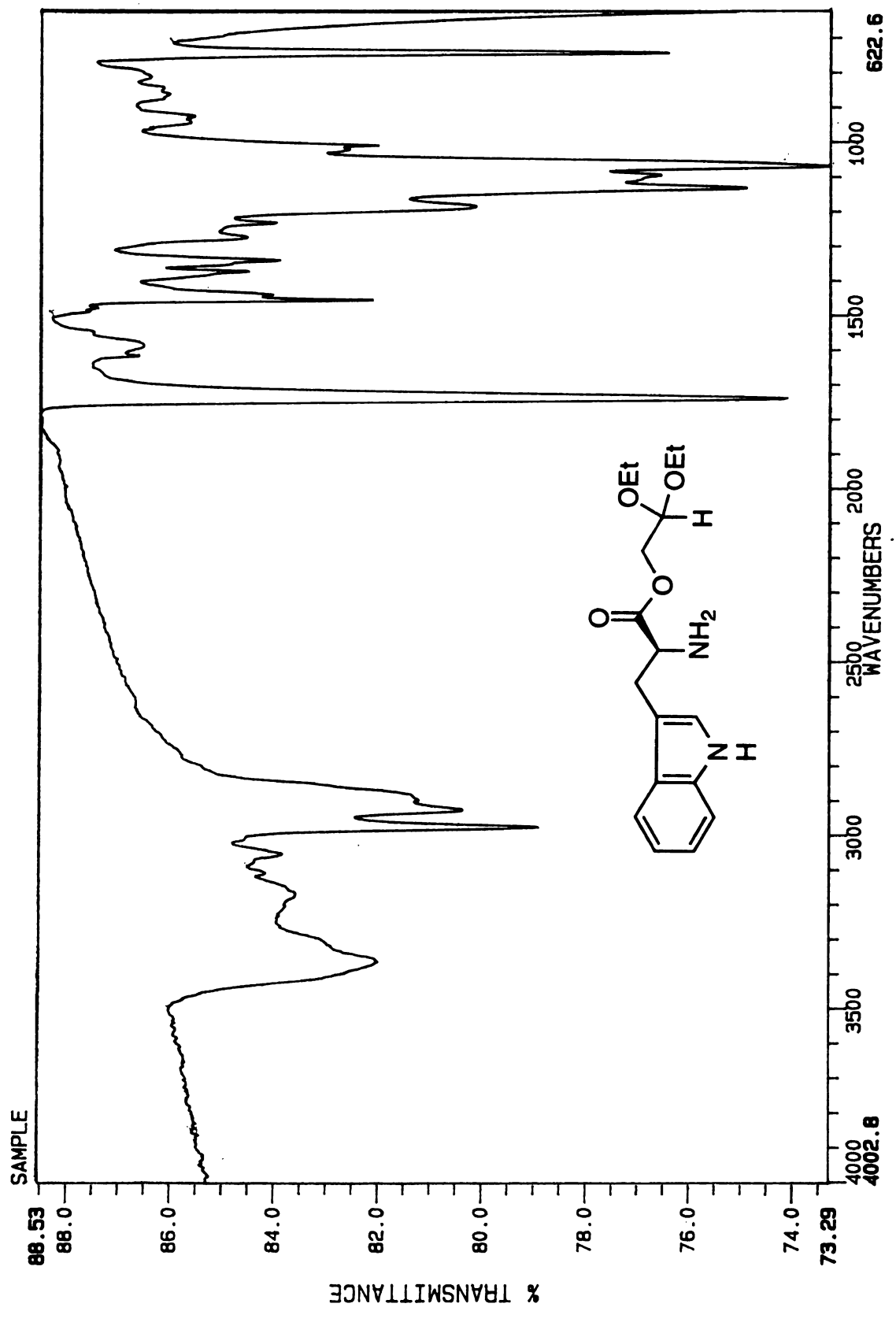


Figure 106 - IR Spectrum of 112

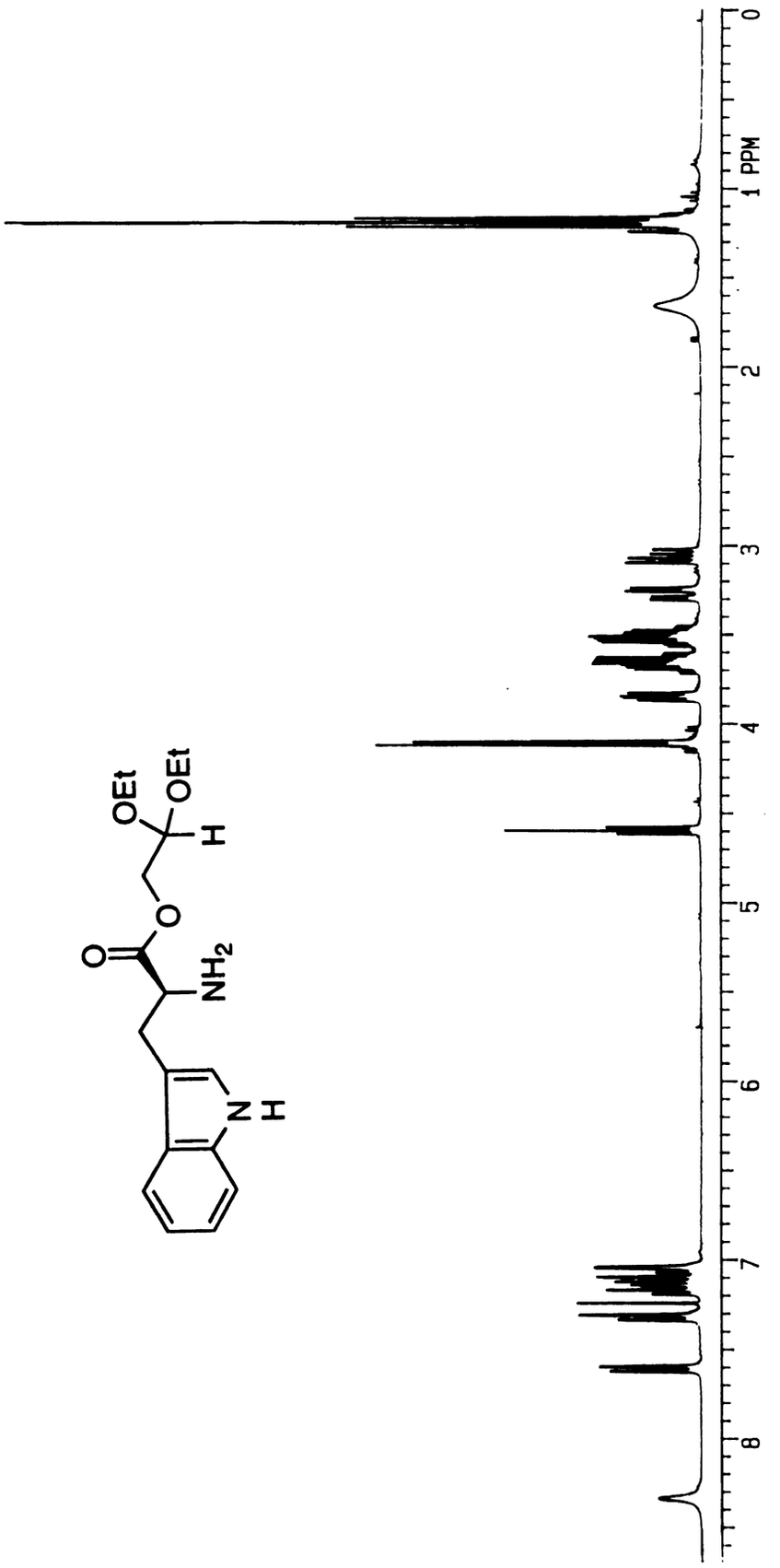


Figure 107 - ^{1}H NMR Spectrum of 112

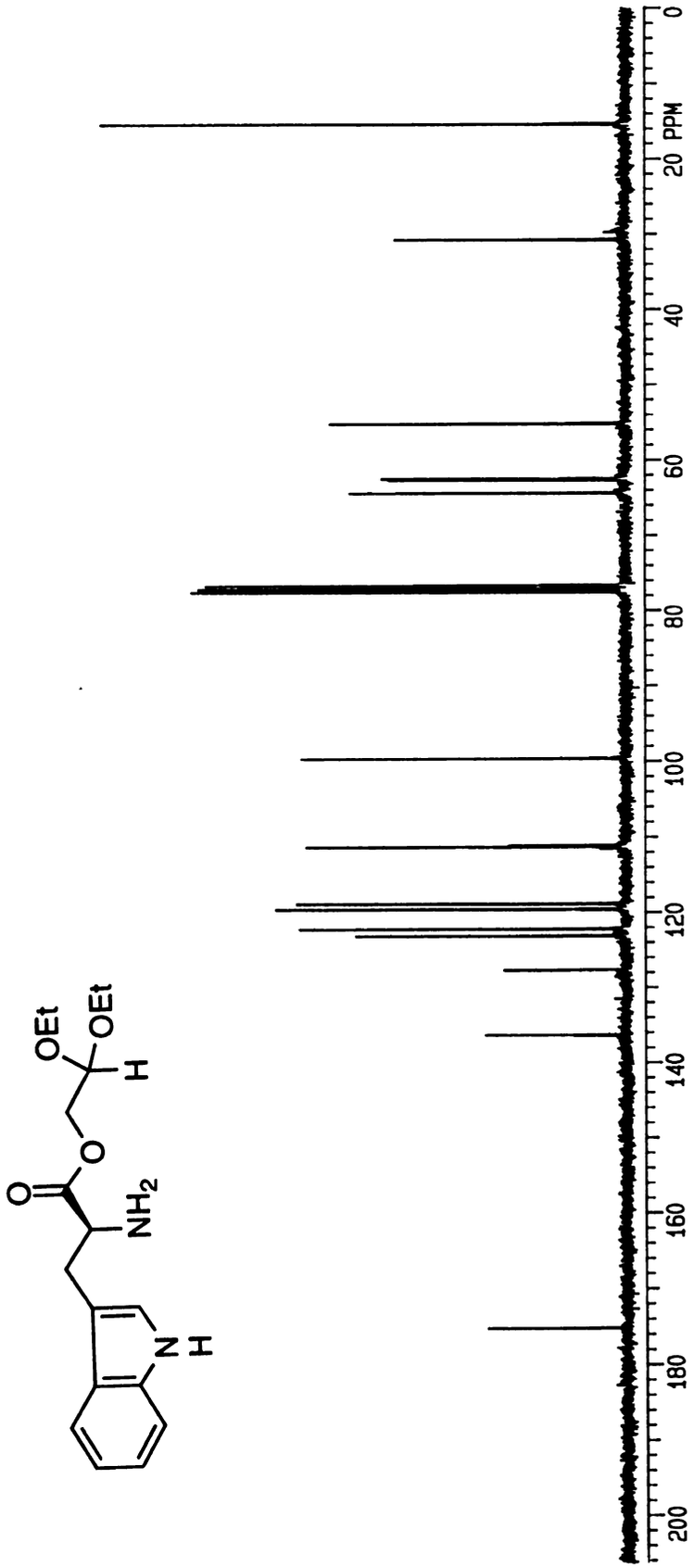


Figure 108 - ^{13}C NMR Spectrum of 112

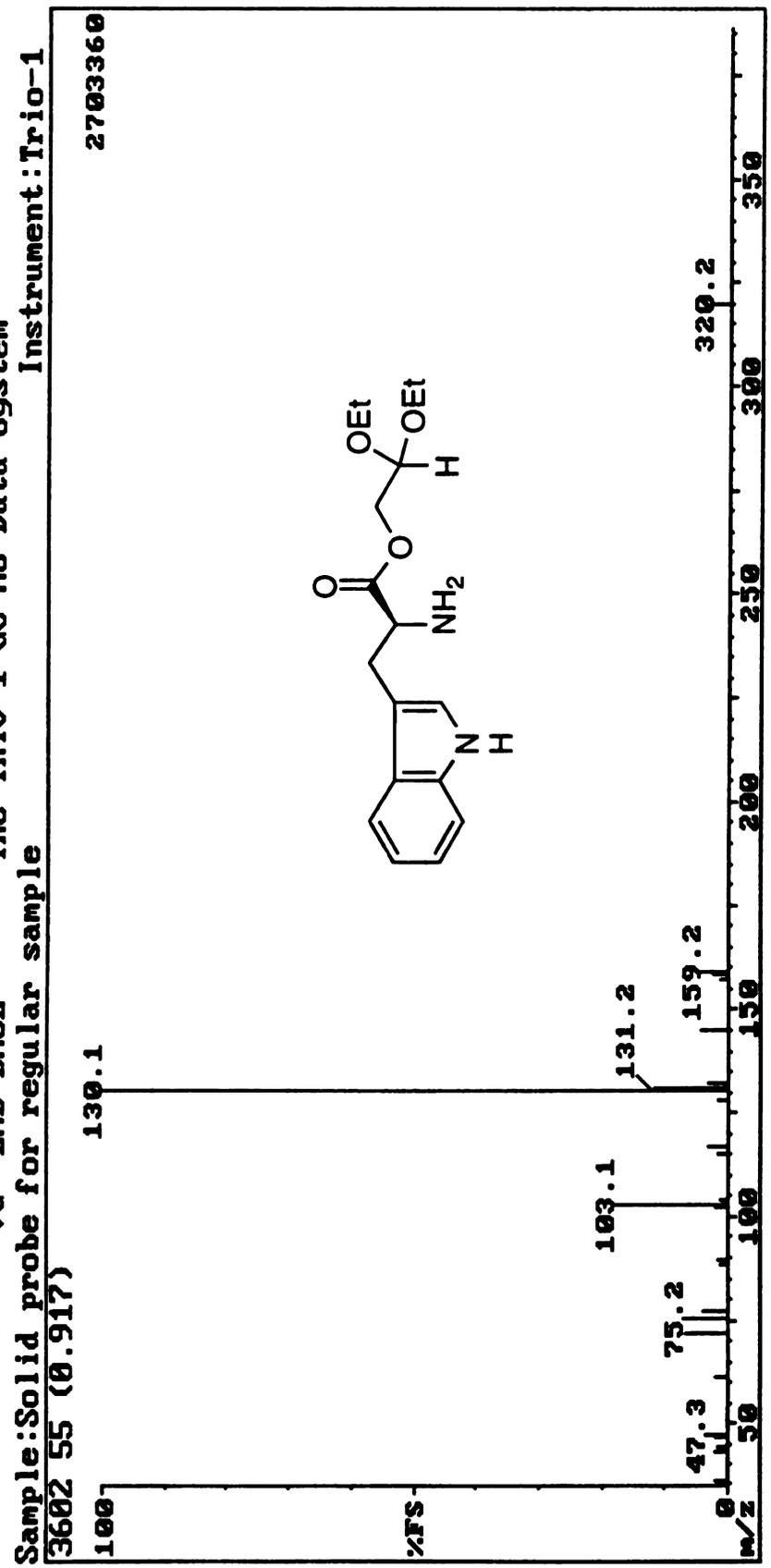


Figure 109 - Mass Spectrum of 112

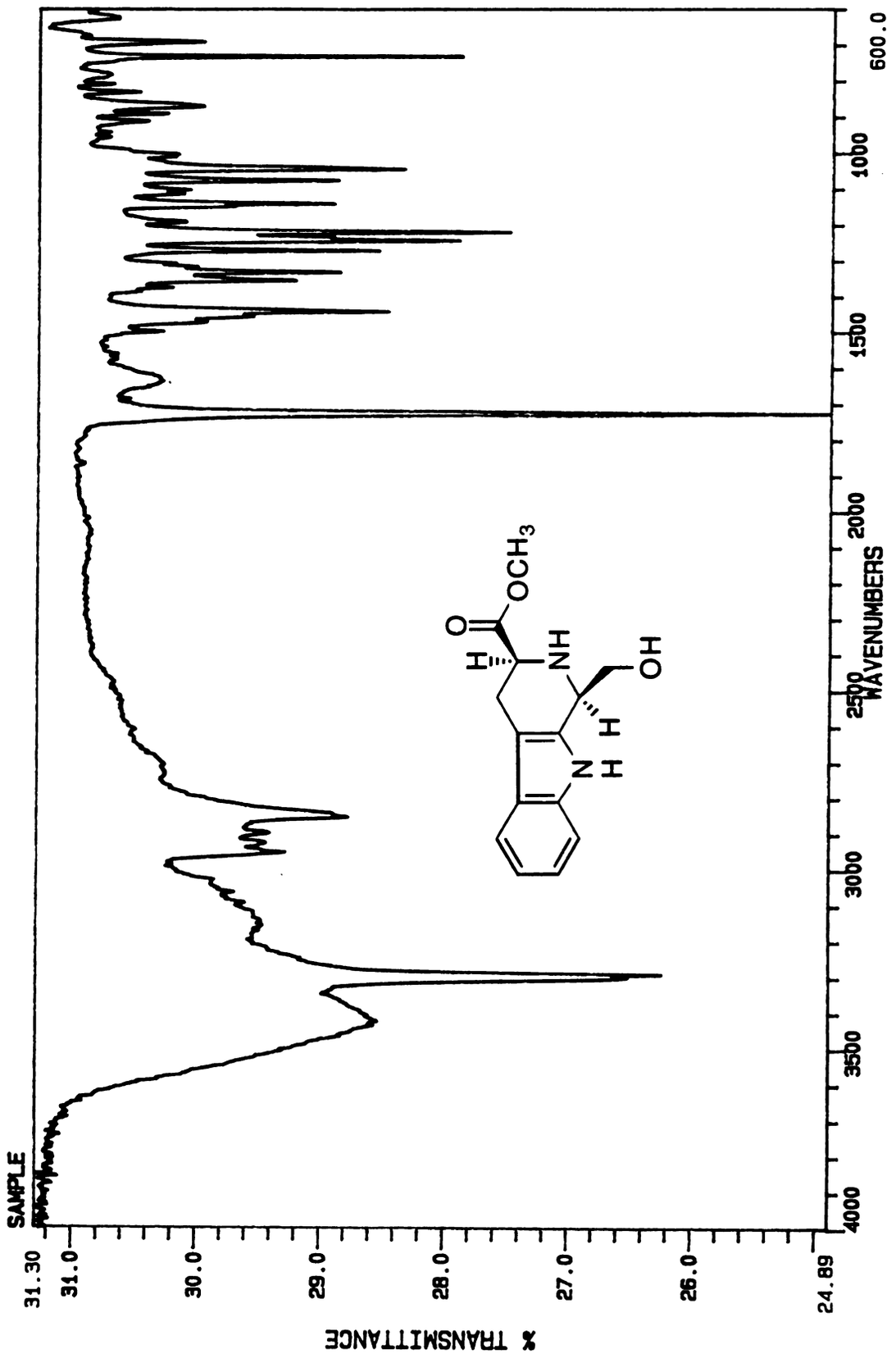


Figure 110 - IR Spectrum of 123a

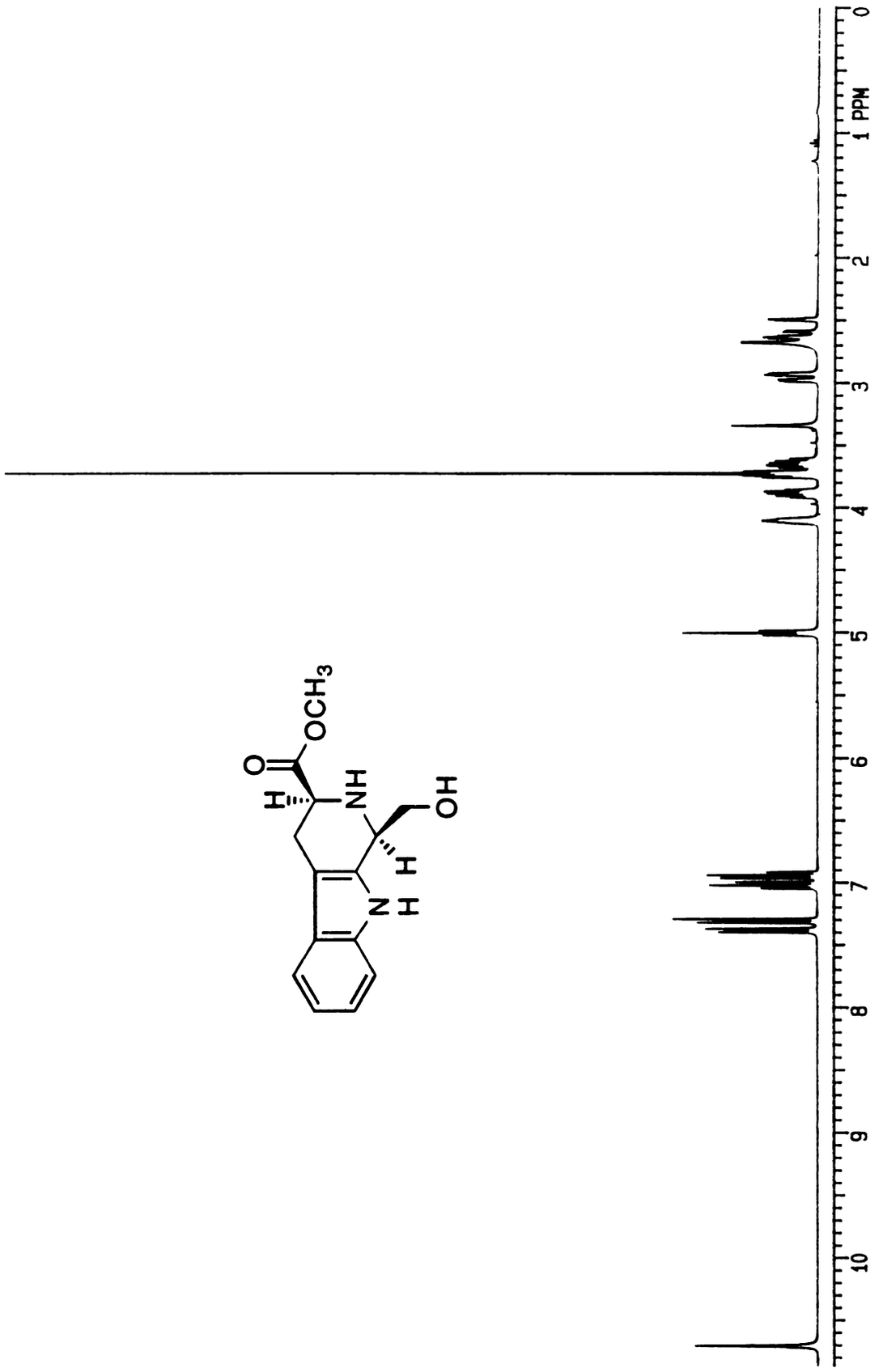


Figure 111 - ^{1}H NMR Spectrum of 123a

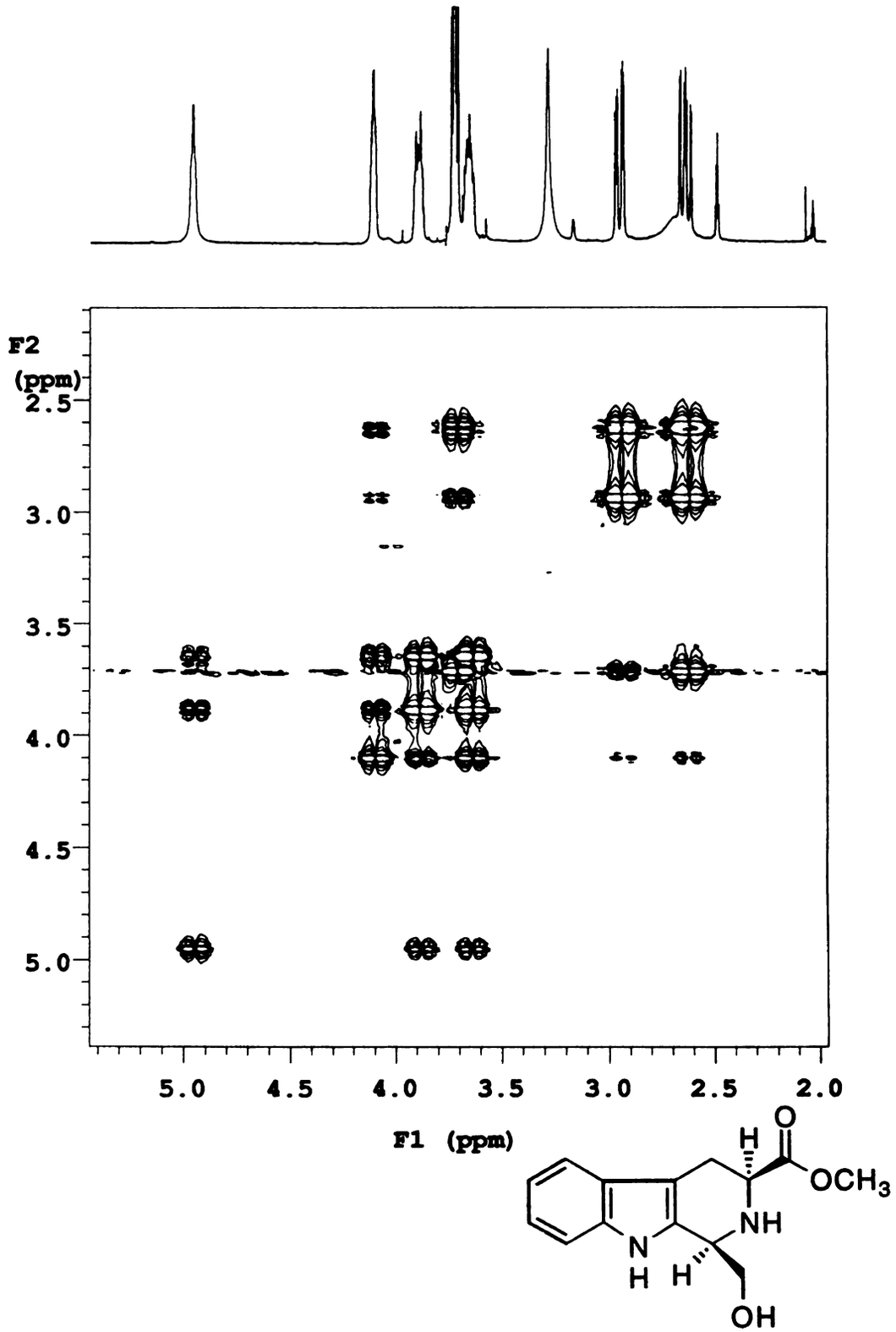


Figure 112 - COSY Spectrum of 123a

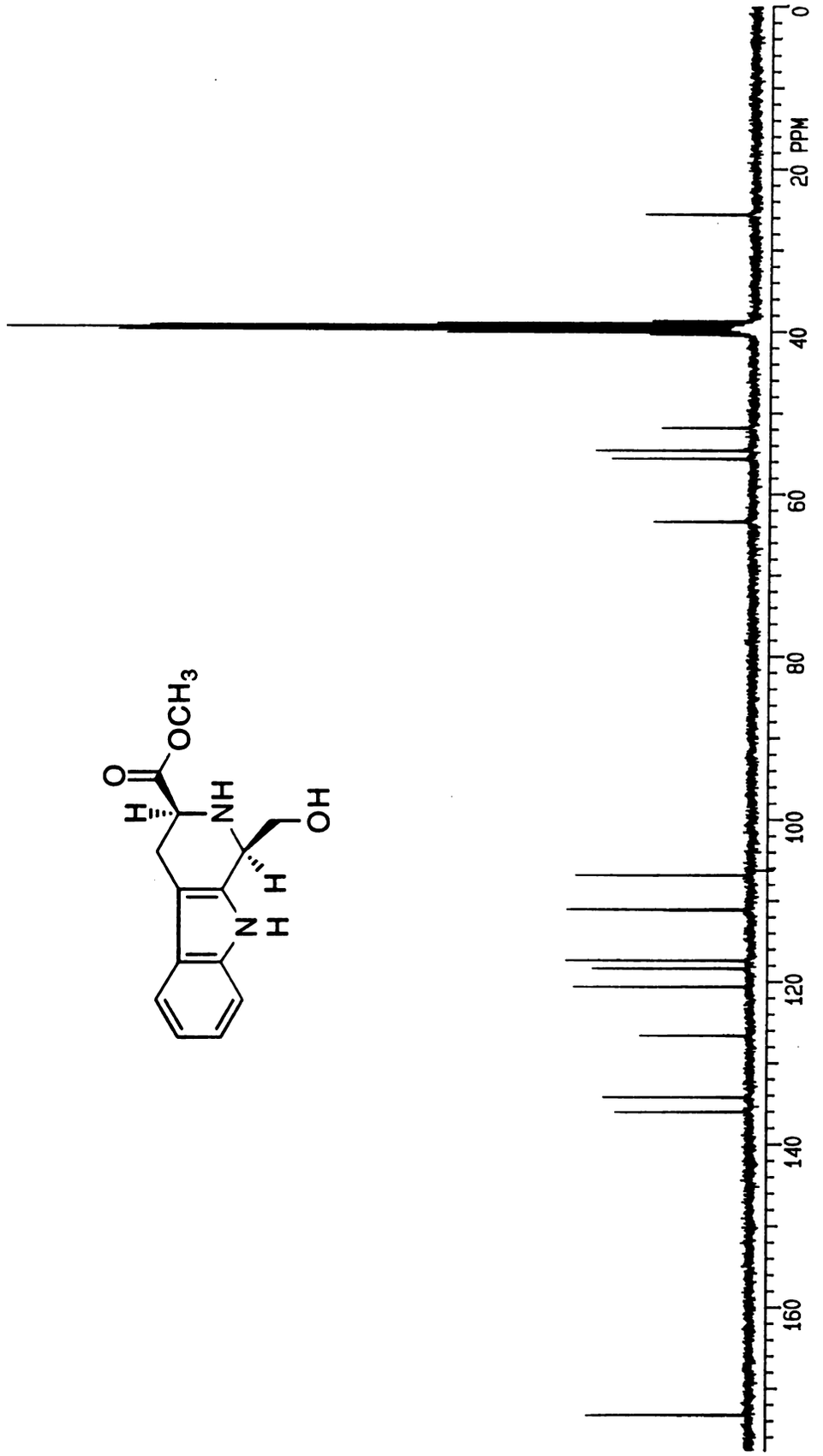


Figure 113 - ^{13}C NMR Spectrum of 123a

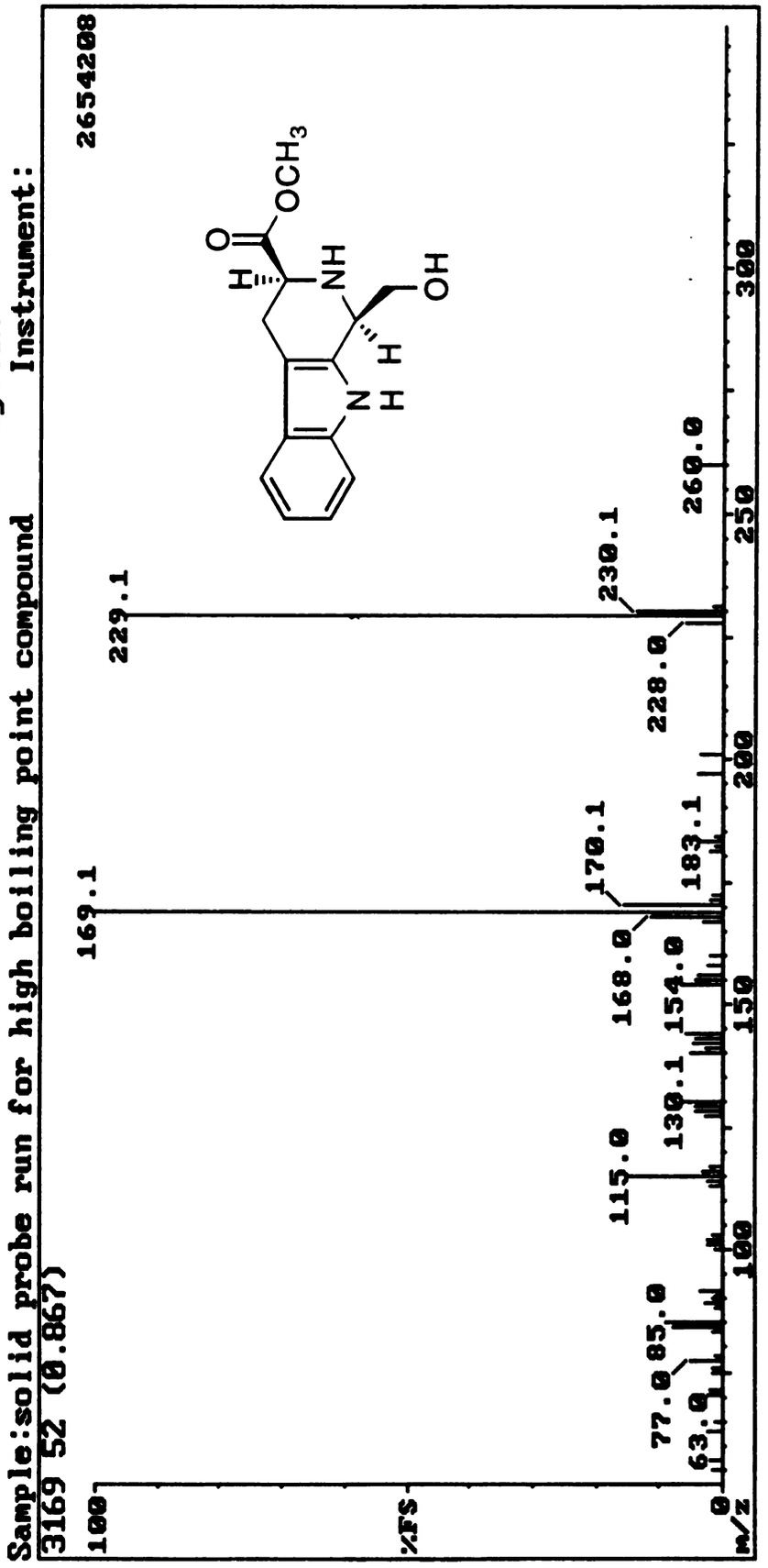


Figure 114 - Mass Spectrum of 123a

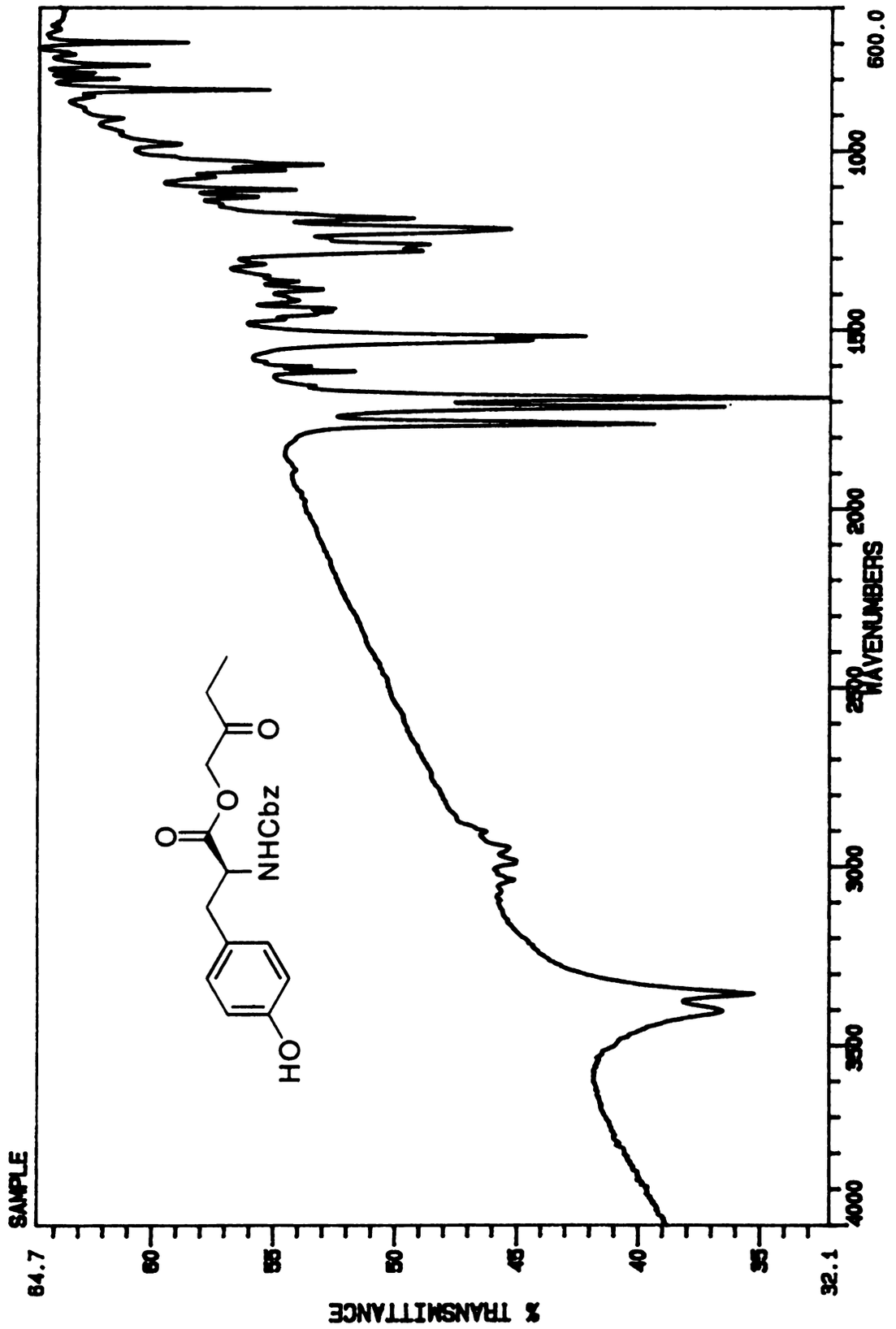


Figure 115 - IR Spectrum of 132

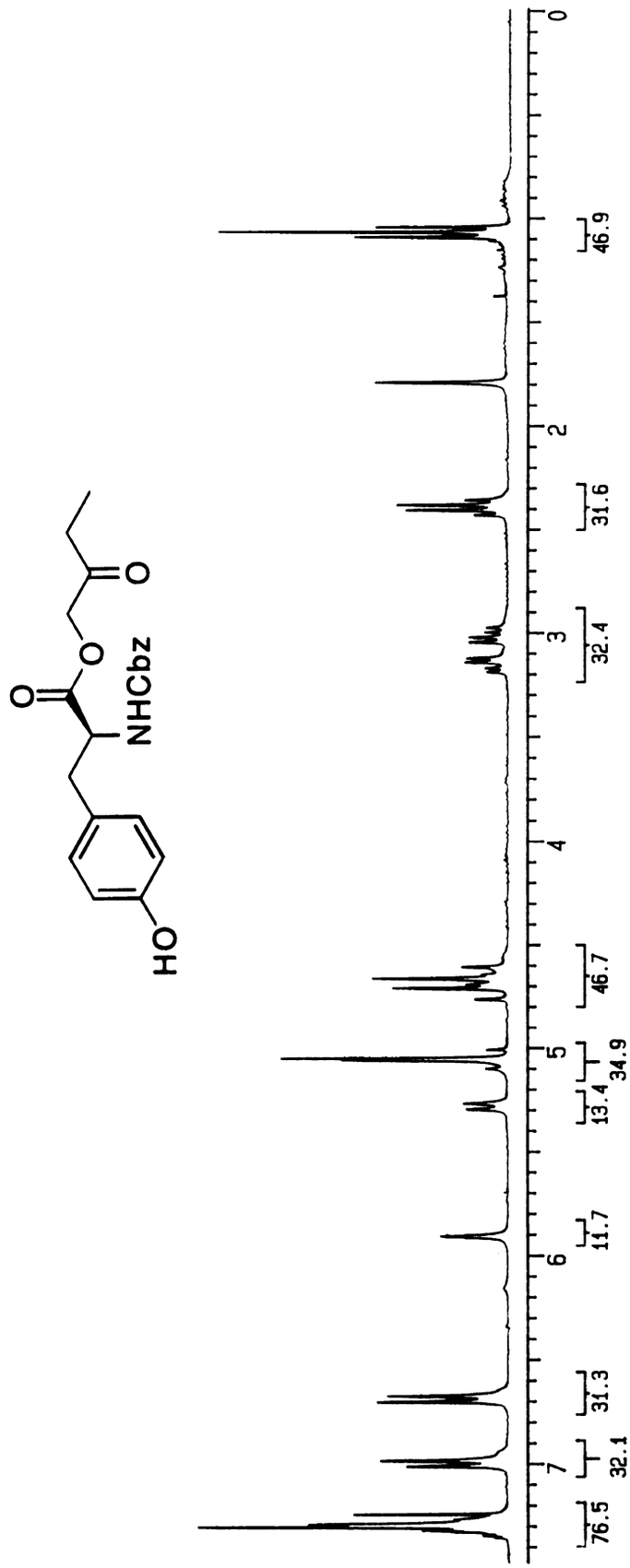


Figure 116 - ^{1}H NMR Spectrum of 132

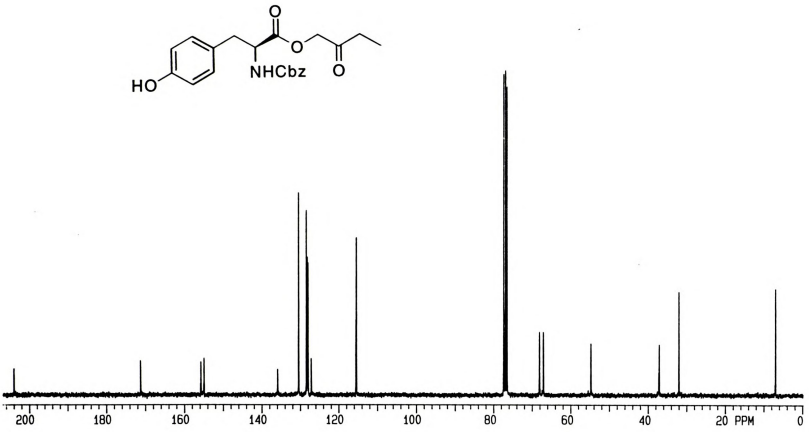
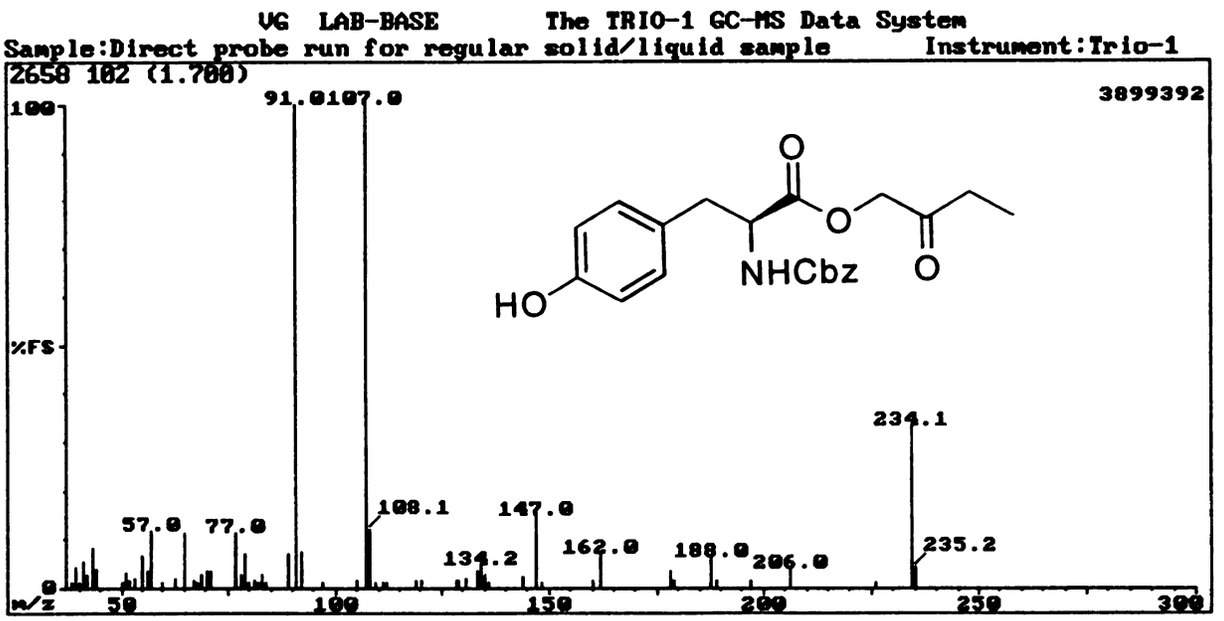


Figure 117 - ^{13}C NMR Spectrum of 132



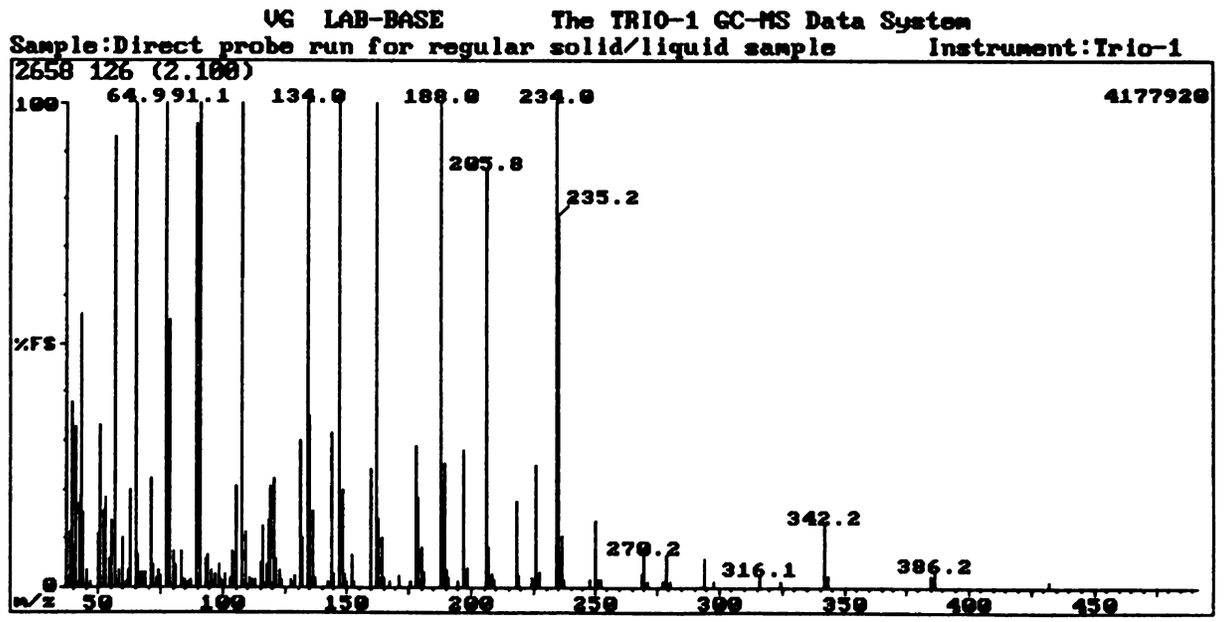


Figure 118 - Mass Spectrum of 132

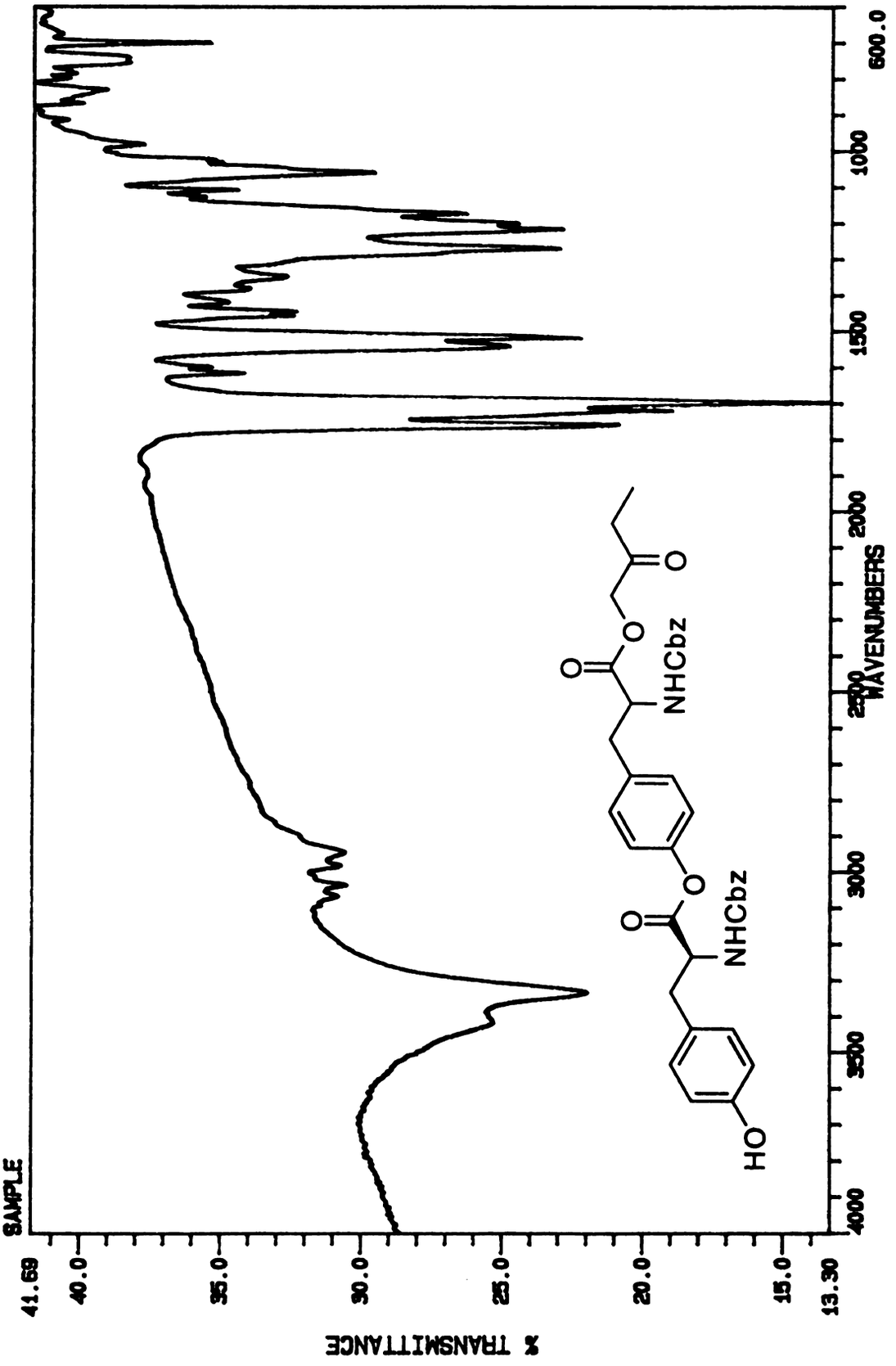


Figure 119 - IR Spectrum of 133

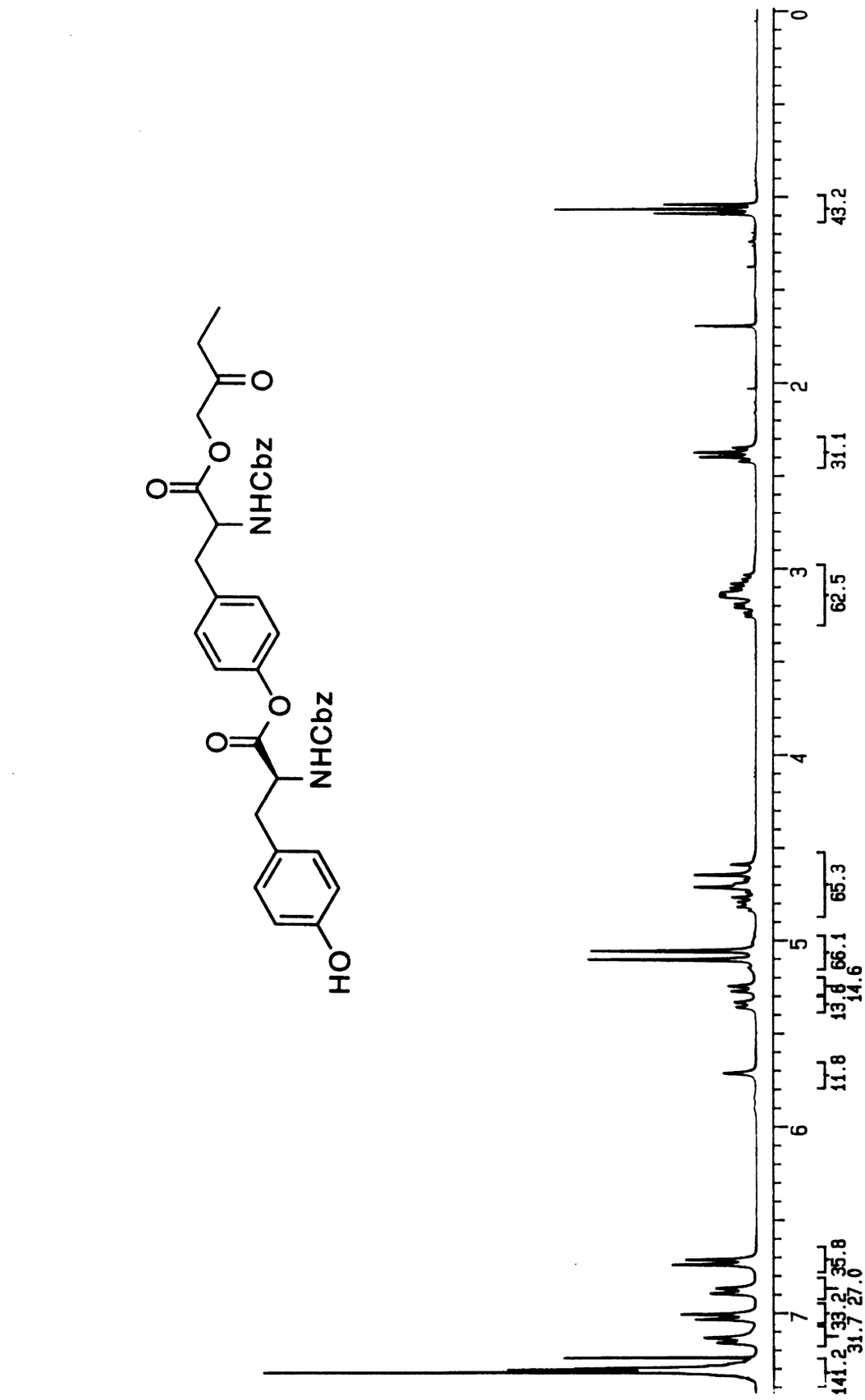


Figure 120 - ^{1}H NMR Spectrum of 133

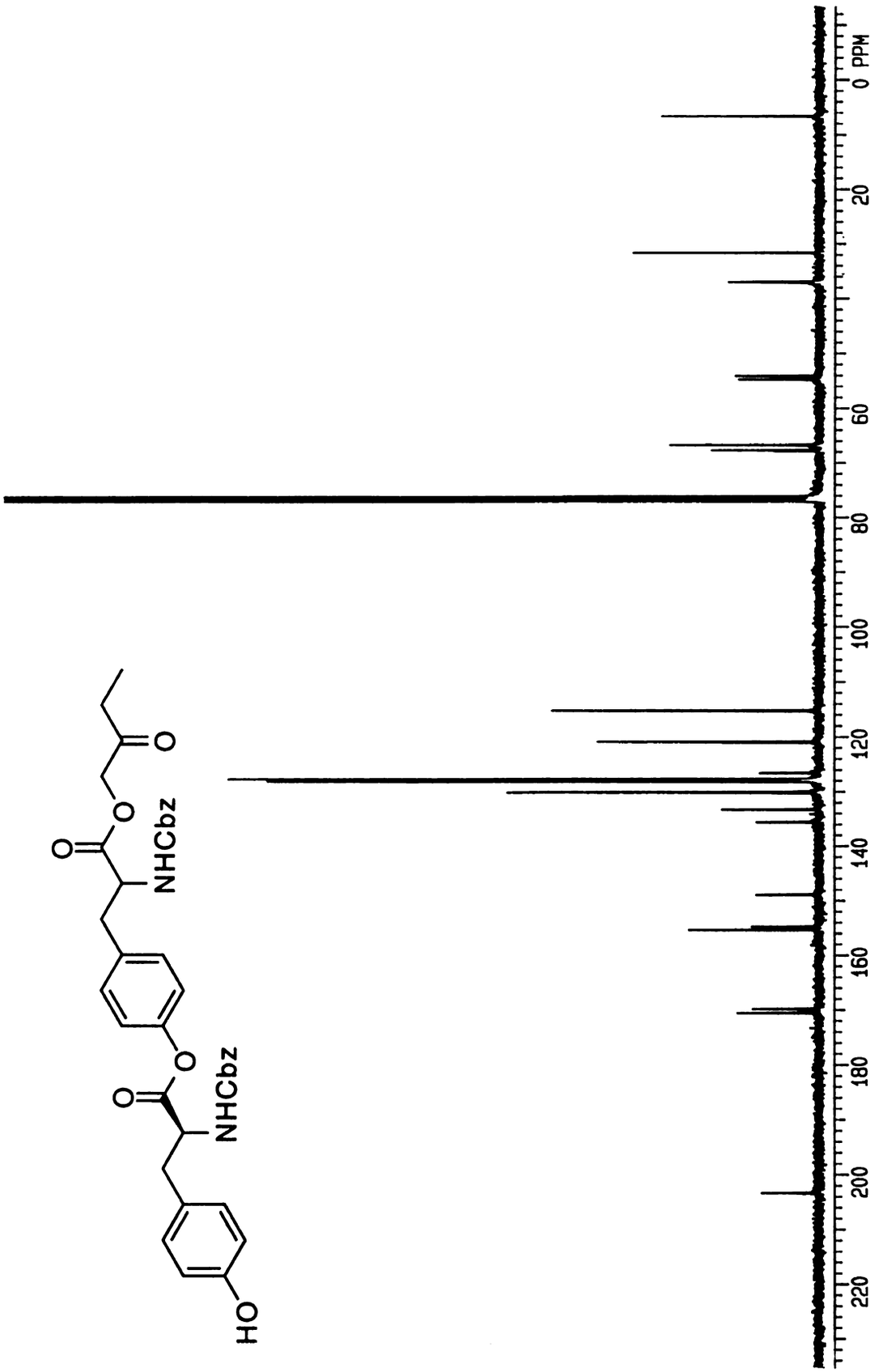


Figure 121 - ^{13}C NMR Spectrum of 133

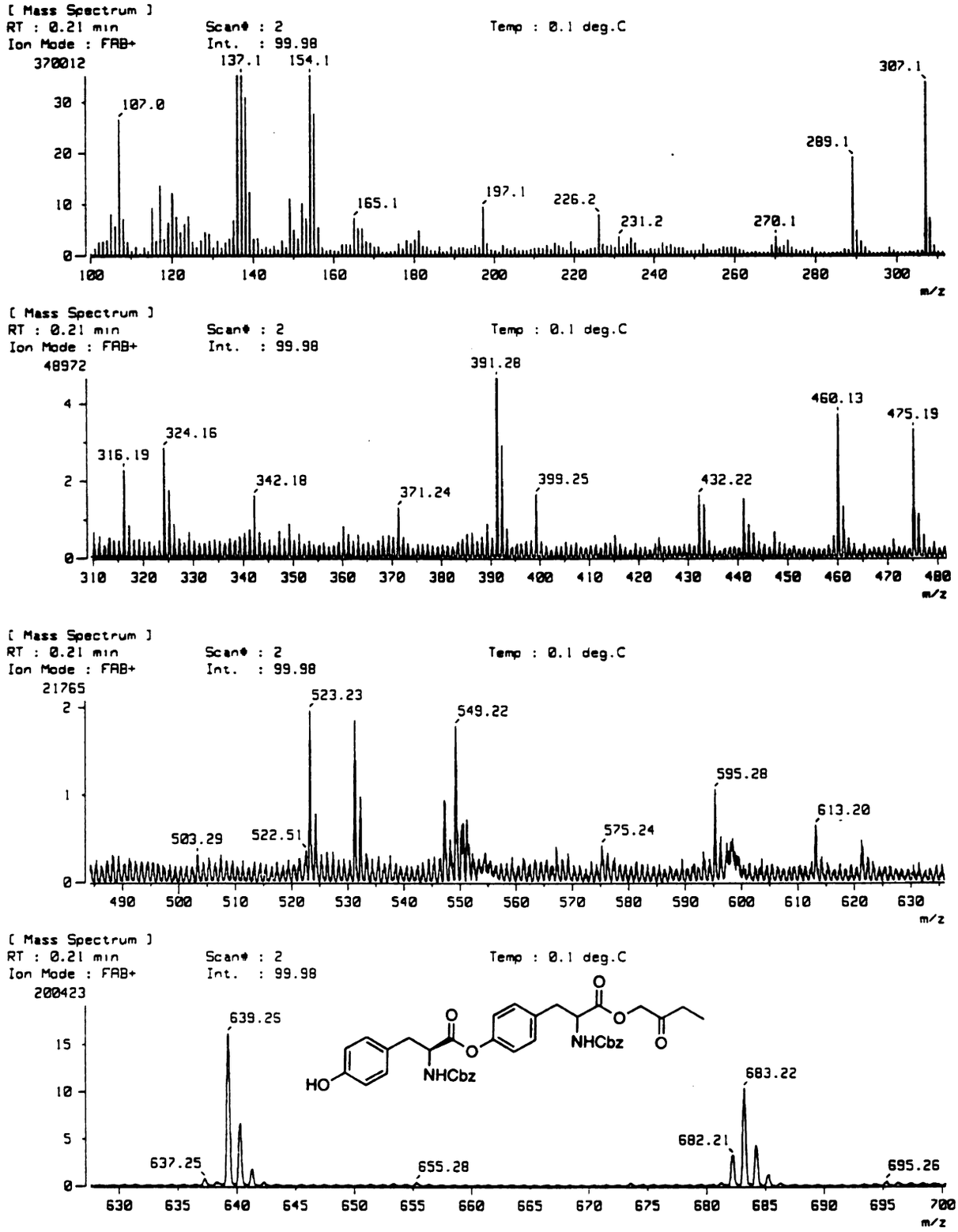


Figure 122 - Mass Spectrum of 133

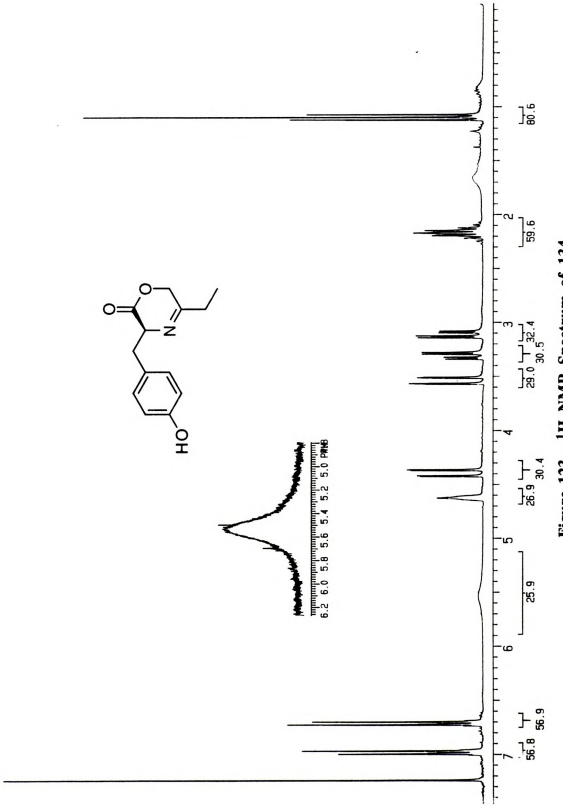


Figure 123 - ^{1}H NMR Spectrum of 134

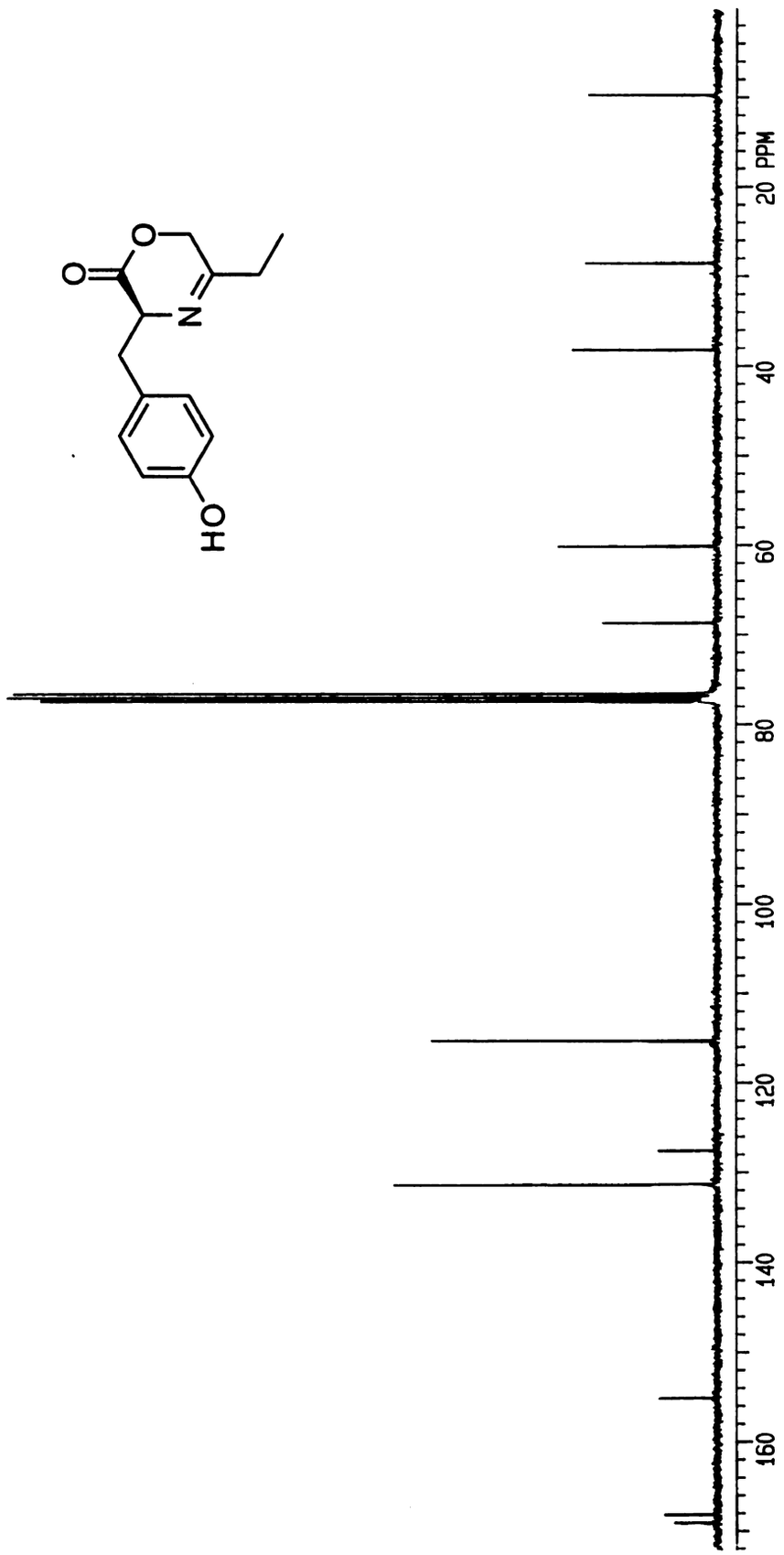


Figure 124 - ^{13}C NMR Spectrum of 134

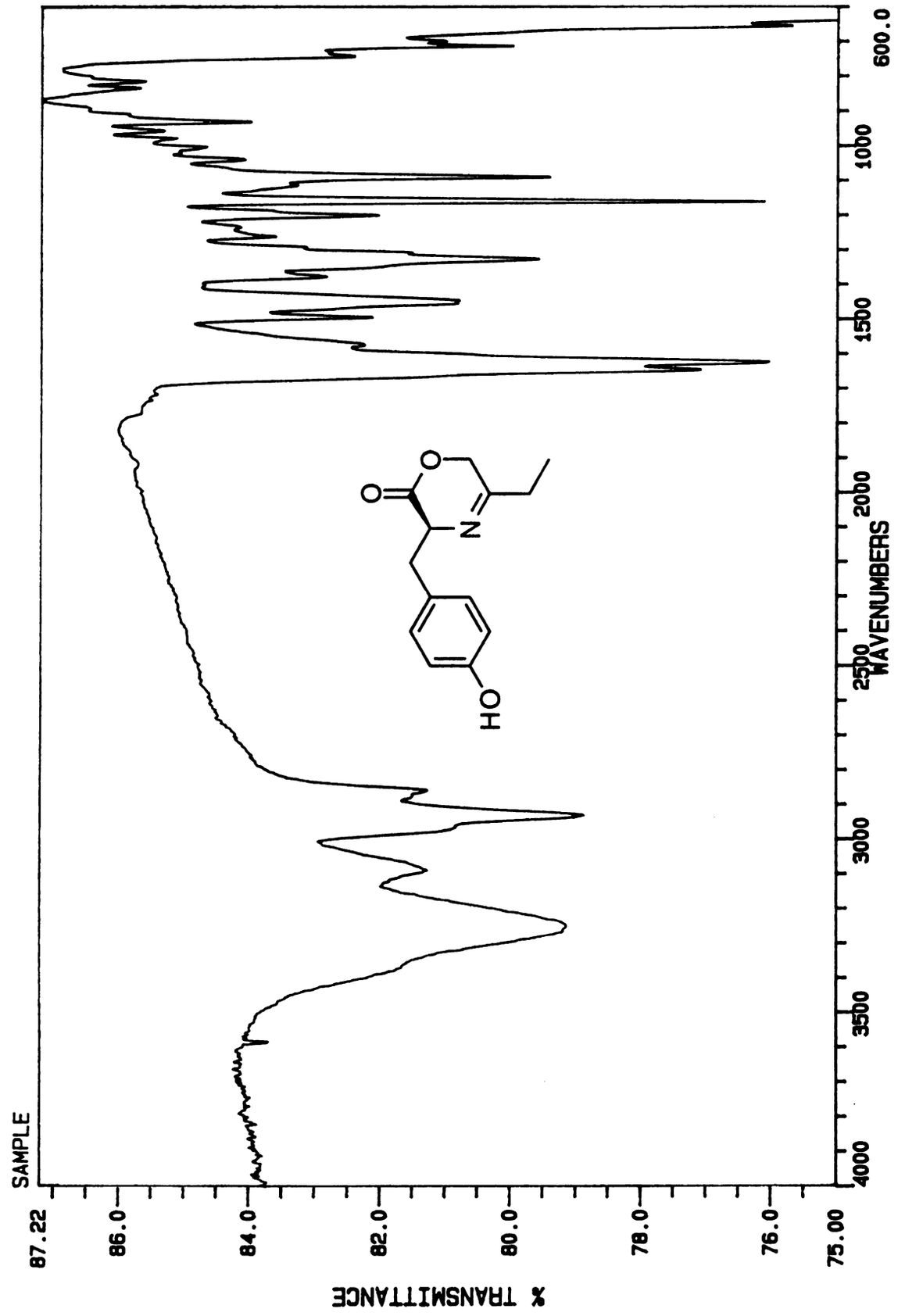


Figure 125 - IR Spectrum of 145

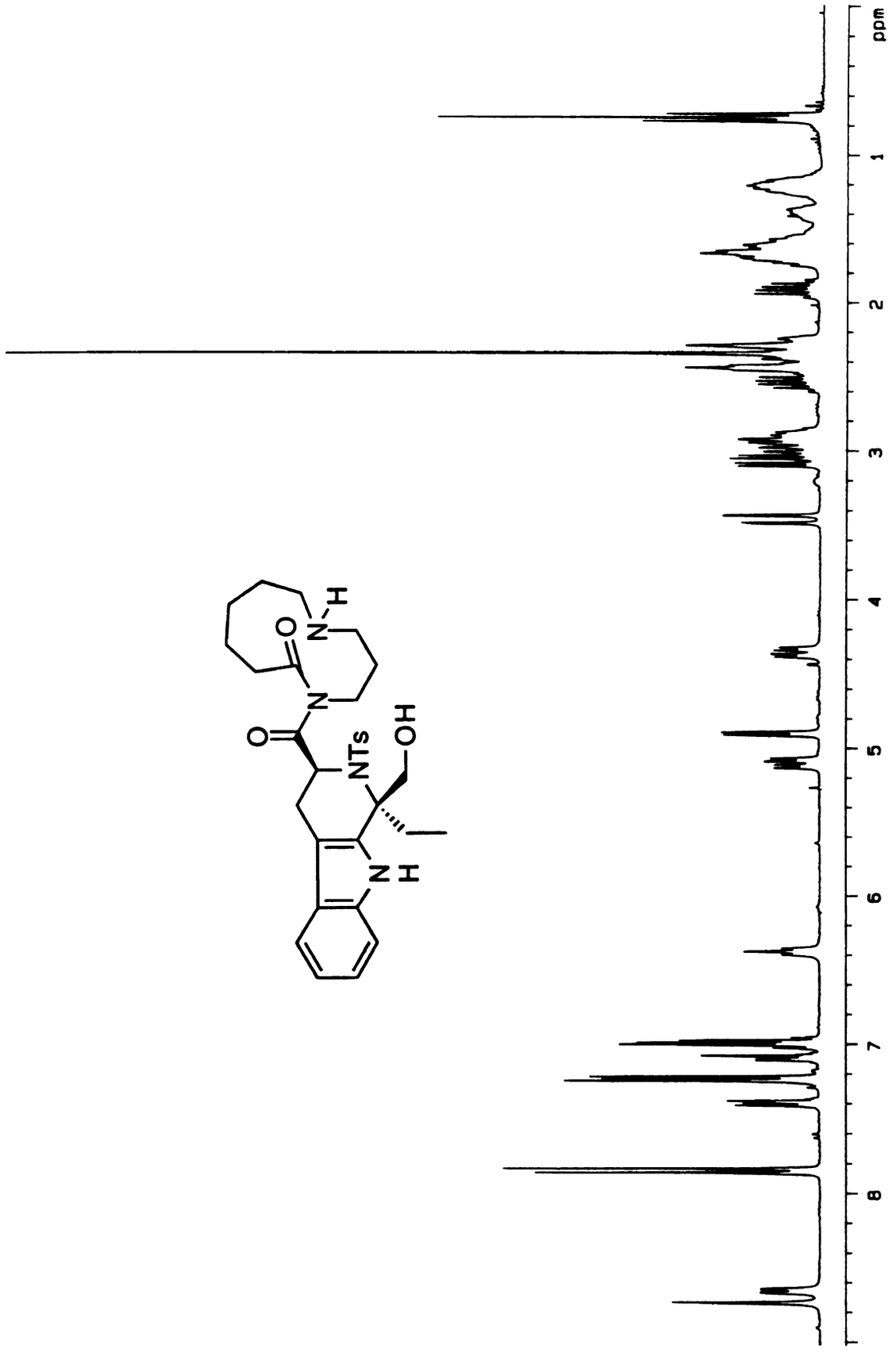


Figure 126 - ^{1}H NMR Spectrum of 145

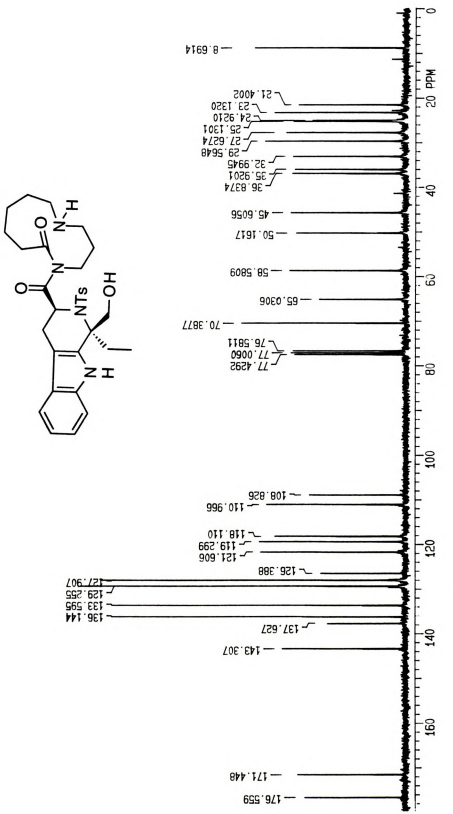


Figure 127 - ^{13}C NMR Spectrum of 145

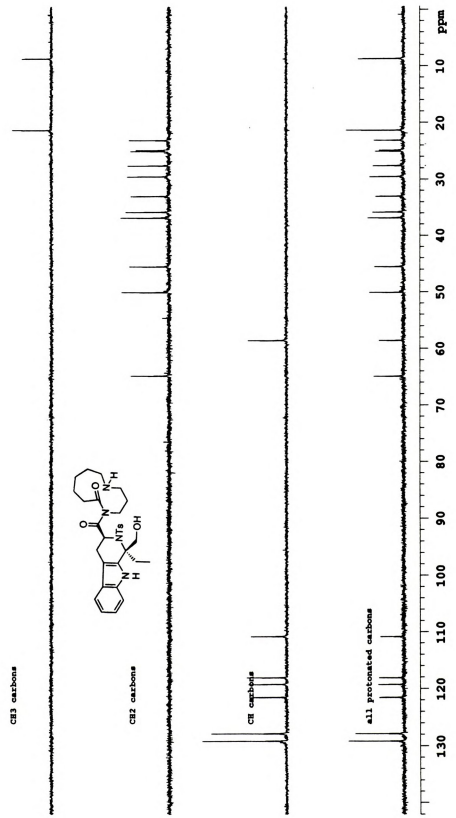


Figure 128 - DEPT Spectrum of 145

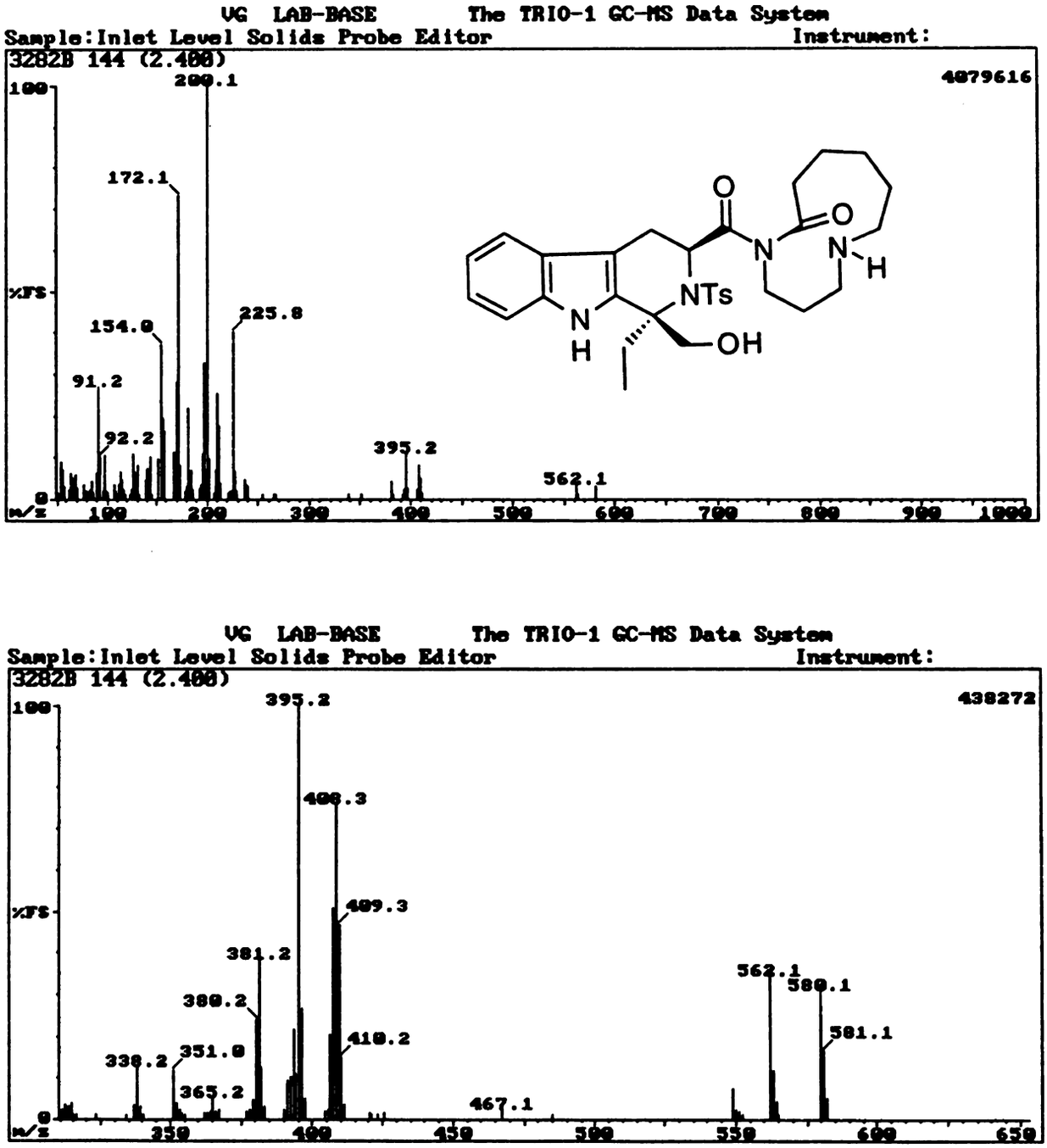


Figure 129 - Mass Spectrum of 145

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