

Acylnitrilium ion-arene spiroannulations : studies toward the synthesis of the Lycopodium alkaloid serratine
by Gregory Randall Luedtke

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
© Copyright by Gregory Randall Luedtke (1994)

Abstract:
The use of C-acylnitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic Lycopodium alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

ACYLNITRILIUM ION - ARENE SPIROANNULATIONS: STUDIES TOWARD THE SYNTHESIS OF THE *LYCOPODIUM* ALKALOID SERRATINE

by

Gregory Randall Luedtke

A thesis submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana
December, 1994

D378
L9675

APPROVAL

of a thesis submitted by

Gregory Randall Luedtke

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

December 13, 1994
Date

Tom
Chairperson, Graduate Committee

Approved for the Major Department

12/14/94
Date

David M Dooley
Head, Major Department

Approved for the College of Graduate Studies

12/16/94
Date

R L Brown
Graduate Dean

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a doctoral degree at Montana State University, I agree that the Library shall make it available to borrowers under rules of the Library. I further agree that copying of this thesis is allowable only for scholarly purposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for extensive copying or reproduction of this thesis should be referred to University Microfilms International, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom I have granted "the exclusive right to reproduce and distribute copies of the dissertation in and from microfilm and the right to reproduce and distribute by abstract in any format."

Signature Gregory A. Luedt

Date 12/13/94

Dedicated to the memory of my father, Randall Harvey Luedtke, and my grandfathers, Harvey August Luedtke and Marvin Draeger Hayes. They were all with me at the beginning of my college schooling, I only wish they could have been here with me at the end.

ACKNOWLEDGMENTS

I wish to thank my entire family for their unending support of me in all my endeavors in school and out. Without this foundation and all that springs from it, I could not have made this accomplishment. My mother and stepfather deserve special acknowledgments. Their loving care was the major reason that I have come this far in life. Words alone are not enough to say how much I appreciate all they have done for me.

There have been many, many co-workers I have encountered in my time here, far too many to list. Let me just say thank you to all who have helped me--you know who you are. Professor Livinghouse served as an excellent supervisor. He gave me free rein in my research on many occasions, which helped me learn all that much more in my time here. But he also reined me in from time to time, or else I may never have gotten out. For all of this and more he has received my utmost admiration.

Professor Ted Bartlett of Fort Lewis College was my original inspiration in the field of chemistry. He remains my idol and gives meaning to the phrase "....to obtain Tedness".

Also many thanks to my many friends who have been with me through the thick and thin, the good and bad of my life here in graduate school.

Finally I wish to thank the Lord our God for giving a Wisconsin farm boy like me the talents that I have.

TABLE OF CONTENTS

Page

INTRODUCTION 1

BACKGROUND 5

Nature of *Lycopodium* Alkaloids 17

Previous Syntheses of *Lycopodium* Alkaloids with the Serratinane Skeleton 22

RESULTS AND DISCUSSION 26

Methods Development 26

Studies Toward the Synthesis of Serratine 29

CONCLUSION 56

EXPERIMENTAL 57

4-*t*-Butyldimethylsilyloxybenzaldehyde (**18a**) 59

2-Methoxy-4-*t*-butyldimethylsilyloxybenzaldehyde (**18b**) 59

3-Methoxy-4-*t*-butyldimethylsilyloxybenzaldehyde (**18c**) 59

4-*t*-Butyldimethylsilyloxycinnamonitrile (**19a**) 60

2-Methoxy-4-*t*-butyldimethylsilyloxycinnamonitrile (**19b**) 60

3-Methoxy-4-*t*-butyldimethylsilyloxycinnamonitrile (**19c**) 61

3,4-Methylenedioxycinnamonitrile (**19d**) 61

2-(4-t-Butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (**20a**) 61

2-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (**20b**) . . 62

2-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (**20c**) . . 62

2-(3,4-Methylenedioxyphenyl)-eth-1-ylnitrile (**20d**) 63

3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylamine (**21a**) 63

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylamine (**21b**) . 64

TABLE OF CONTENTS--Continued

Page

3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylamine (**21c**) . 64

3-(3,4-Methylenedioxyphenyl)-prop-1-ylamine (**21d**) 65

N-[3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (**22a**) . . 65

N-[3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (**22b**) 66

N-[3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (**22c**) 66

N-[3,4-Methylenedioxyphenyl)-prop-1-yl]formamide (**22d**) 67

3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23a**) 67

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23b**) 68

3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23c**) 68

3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (**23d**) 69

7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25a**) 69

1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25b**) 70

1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (**25c**) 71

1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (**25d**) 71

1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**27**) 72

3-(Prop-1-ene)-phenol (**29**) 72

3-(Prop-2-enoxy)-*t*-butyldimethylsilyloxyphenol (**30**) 73

TABLE OF CONTENTS--Continued

Page

3-[4-*t*-Butyldimethylsilyloxy)phen-2-ol]-prop-1-ene (**31**) 74

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ene (**32**) . . . 74

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)propan-1-ol (**33**) . . . 75

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-methanesulphonyl-propane (**34**) 76

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-propane azide (**35**) 76

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-propane imine (**37**) 77

1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (**38**) 78

1-Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**40**) 78

1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**42**) 79

Phenylthio tricycle (**43**) 80

N-Methyl-2-phenyl-pyrrolidine (**45**) 81

1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**51**) 81

Methylthio tricycle (**52**) 82

REFERENCES 84

APPENDIX 89

LIST OF TABLES

Table		Page
1	Unsuccessful Attempts to Functionalize Spirocycle **27**	34

LIST OF FIGURES

Figure		Page
1	Serratine (**1**)	17
2	Major Skeletal Classes of *Lycopodium* Alkaloids.	18
3	Representative Alkaloids within the Species *Lycopodium* serratum Thumb.	19
4	Blocking Effect of the Trimethylsilyl Moiety to Nucleophilic Addition and to Leaving Group in **57**.	53
5	^{1}H NMR Spectrum of 3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23a**)	90
6	^{13}C NMR Spectrum of 3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23a**)	91
7	^{1}H NMR Spectrum of 3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23b**)	92
8	^{13}C NMR Spectrum of 3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23b**)	93
9	^{1}H NMR Spectrum of 3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23c**)	94
10	^{13}C NMR Spectrum of 3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23c**)	95
11	^{1}H NMR Spectrum of 3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (**23d**)	96
12	^{13}C NMR Spectrum of 3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (**23d**)	97

LIST OF FIGURES--Continued

Figure		Page
13	^{1}H NMR Spectrum of 7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25a**)	98
14	^{13}C NMR Spectrum of 7-Trimethylacetyl-8-azaspiroundeca-1,4,7- trien-3-one (**25a**)	99
15	^{1}H NMR Spectrum of 1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25b**)	100
16	^{13}C NMR Spectrum of 1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25b**)	101
17	^{1}H NMR Spectrum of 1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2- benzazepine (**25c**)	102
18	^{13}C NMR Spectrum of 1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (**25c**)	103
19	^{1}H NMR Spectrum of 1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (**25d**)	104
20	^{13}C NMR Spectrum of 1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (**25d**)	105
21	^{1}H NMR Spectrum of 1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**27**)	106
22	^{13}C NMR Spectrum of 1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**27**)	107

LIST OF FIGURES--Continued

Figure		Page
23	^{1}H NMR Spectrum of 1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (**38**)	108
24	^{13}C NMR Spectrum of 1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (**38**)	109
25	^{1}H NMR Spectrum of 1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**42**)	110
26	^{13}C NMR Spectrum of 1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**42**)	111
27	^{1}H NMR Spectrum of Phenylthio tricyle (**43**)	112
28	^{13}C NMR Spectrum of Phenylthio tricyle (**43**)	113
29	^{1}H NMR Spectrum of 1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**51**)	114
30	^{13}C NMR Spectrum of 1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**51**)	115
31	^{1}H NMR Spectrum of Methylthio tricyle (**52**)	116
32	^{13}C NMR Spectrum of Methylthio tricyle (**52**)	117
33	^{1}H NMR Spectrum of 1-Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**40**)	118
34	^{13}C NMR Spectrum of 1-Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**40**)	119

ABSTRACT

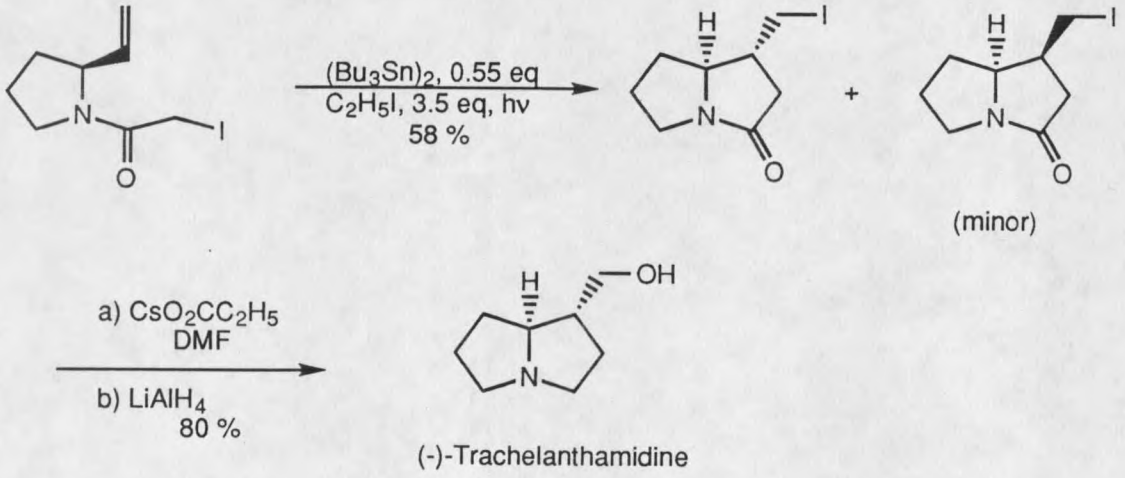
The use of *C*-acylnitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic *Lycopodium* alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

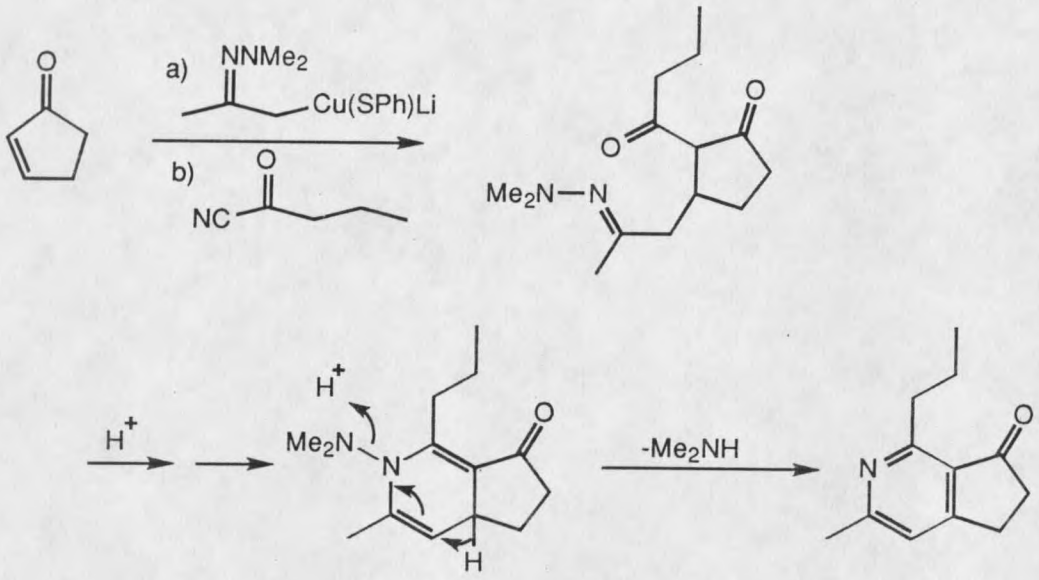
Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

INTRODUCTION

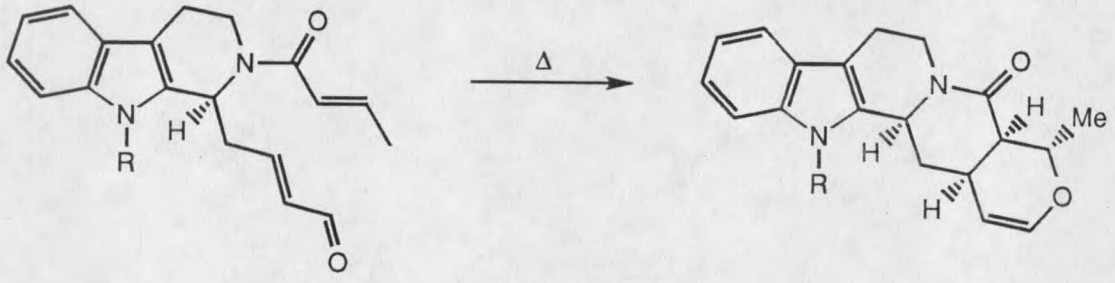
The interest in alkaloids as major synthetic targets has increased in recent years due to a heightened desire to study their biological properties. However, relatively few general methods have been developed for the assembly of nitrogen containing heterocycles. Representative methodologies include: free radical cyclizations, as illustrated by the key step leading to the synthesis of (-)-trachelanthamidine by Jolly and Livinghouse[1] (Eq. 1); anion initiated cyclizations, as utilized by Kelly and Liu[2] in their development of a new pyridine synthesis (Scheme 1); and cycloaddition reactions, as exemplified by Martin in the synthesis of 2- oxindole alkaloids (Eq. 2).[3]



Eq. 1



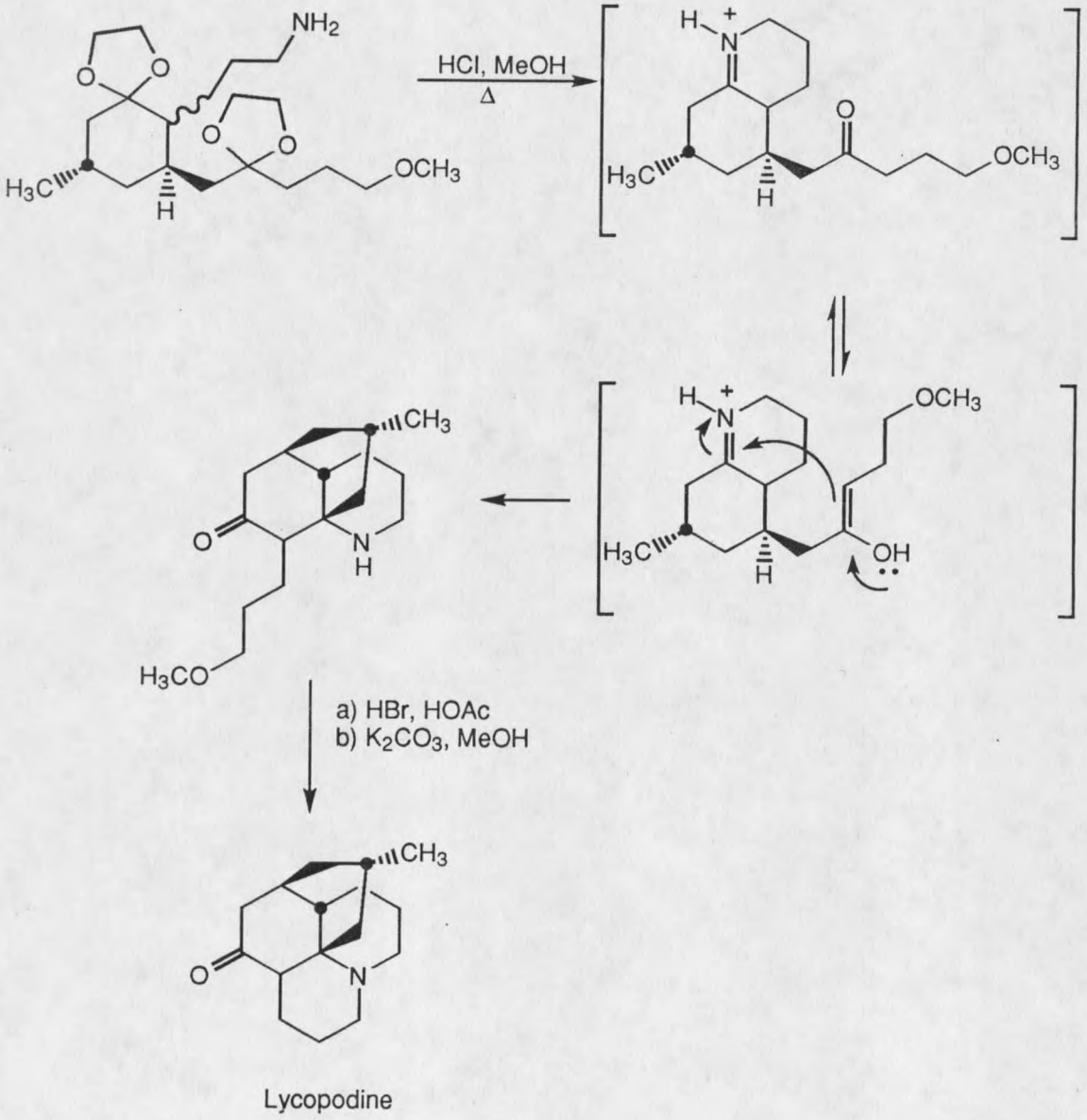
Scheme 1



Eq. 2

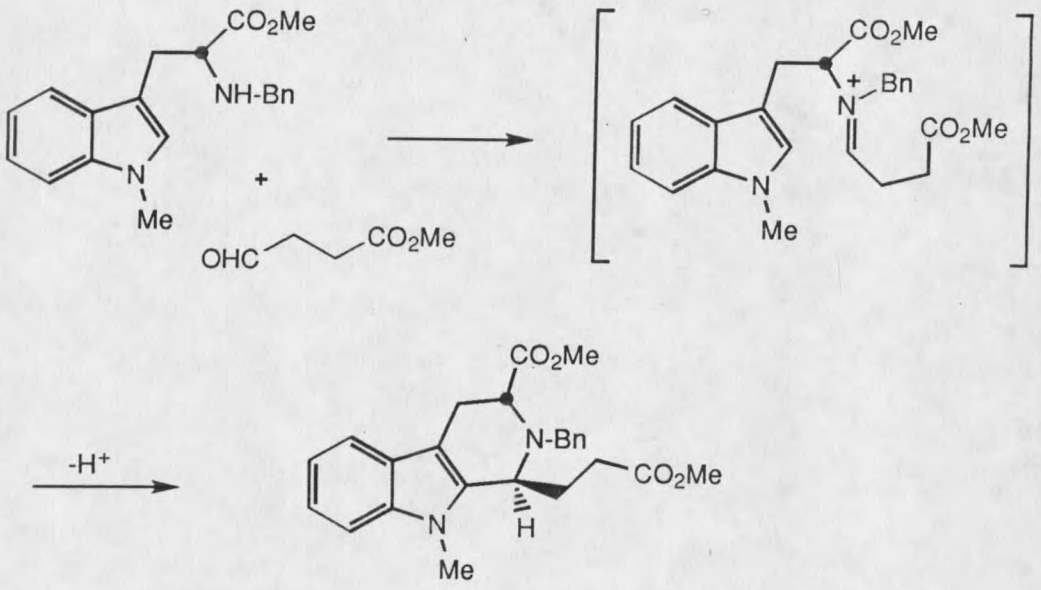
Perhaps the most widely used methods for the synthesis of alkaloids utilize nitrogen stabilized cations as reaction initiators. Some of the earliest methods in this class of reaction involved the use of iminium ions as reactive intermediates. These methods include the Mannich reaction, used by

Heathcock[4] in the synthesis of Lycopodine (Scheme 2), and the Pictet-Spengler reaction, of which the stereochemical aspects were recently examined by Cook[5] (Eq. 3).



Lycopodine

Scheme 2

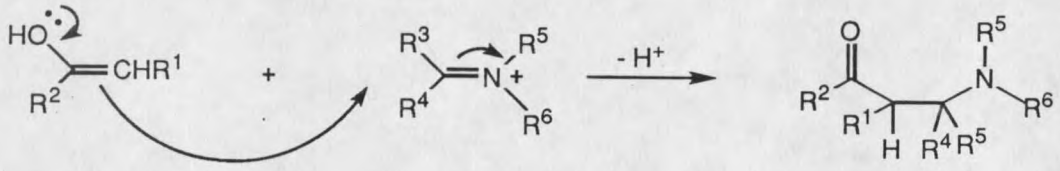


Eq. 3

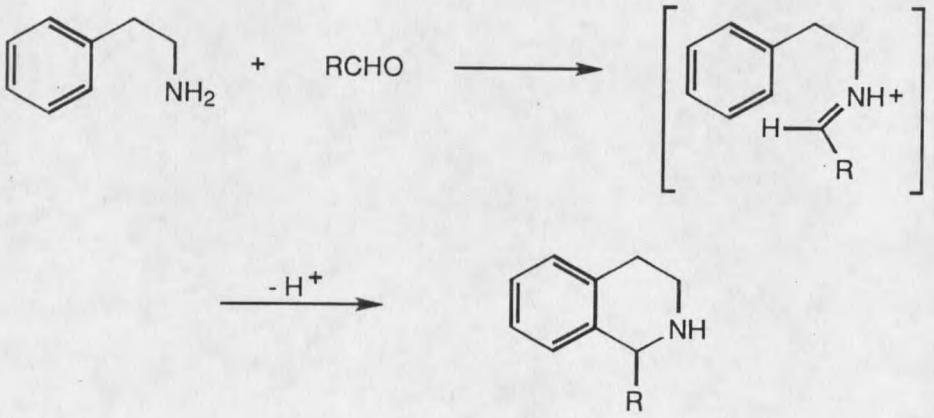
Many developments have occurred in recent years that have extended the use of nitrogen stabilized cations to the synthesis of natural products. However, even with the variety of procedures available, further methods which will facilitate the synthesis of complex heterocycles are needed. The work described herein is an effort toward that end.

BACKGROUND

Nitrogen stabilized cations are very frequently used in the synthesis of azacycles. One commonly used method involves the use of an iminium ion as a reactive intermediate. The most well known reactions of this type include the Mannich reaction, in which an enolizable carbonyl moiety serves as the reaction terminator, and the Pictet-Spengler reaction, in which an aromatic ring acts as the nucleophilic component (Scheme 3 and Eq. 4)

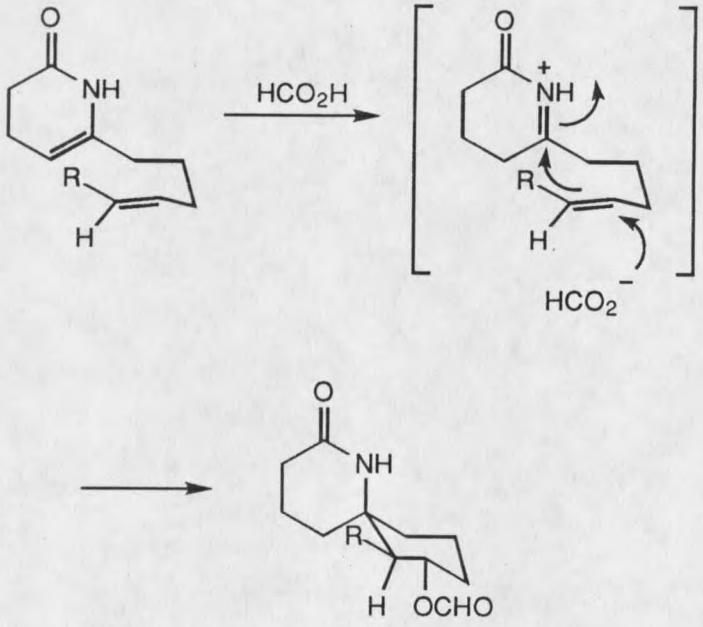


Scheme 3



Eq. 4

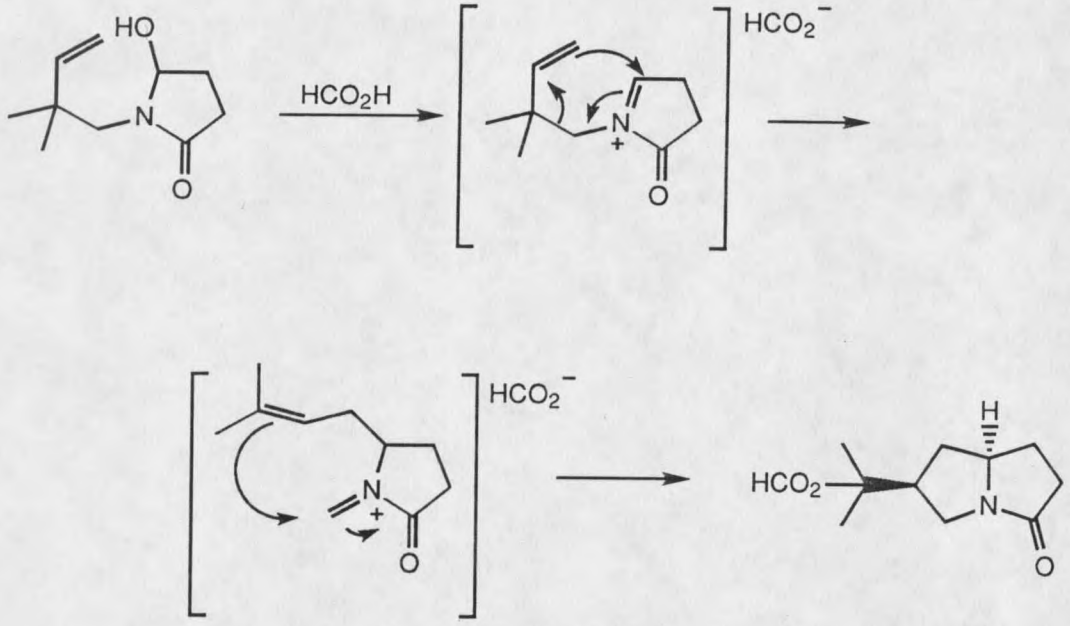
The more reactive *N*-acyliminium ion has been utilized in a manner similar to the iminium ion where aromatic ring system acts as a nucleophile.[6] However, due to its increased reactivity, it was discovered that *N*-acyliminium ions react with a wider range of nucleophiles, including isolated olefins.[7] In such reactions the olefin attacks the electron difficient carbon of the *N*-acyliminium ion while another nucleophile present during the reaction, typically the conjugate base of the acid used to form the active species adds to the olefin (Scheme 4).



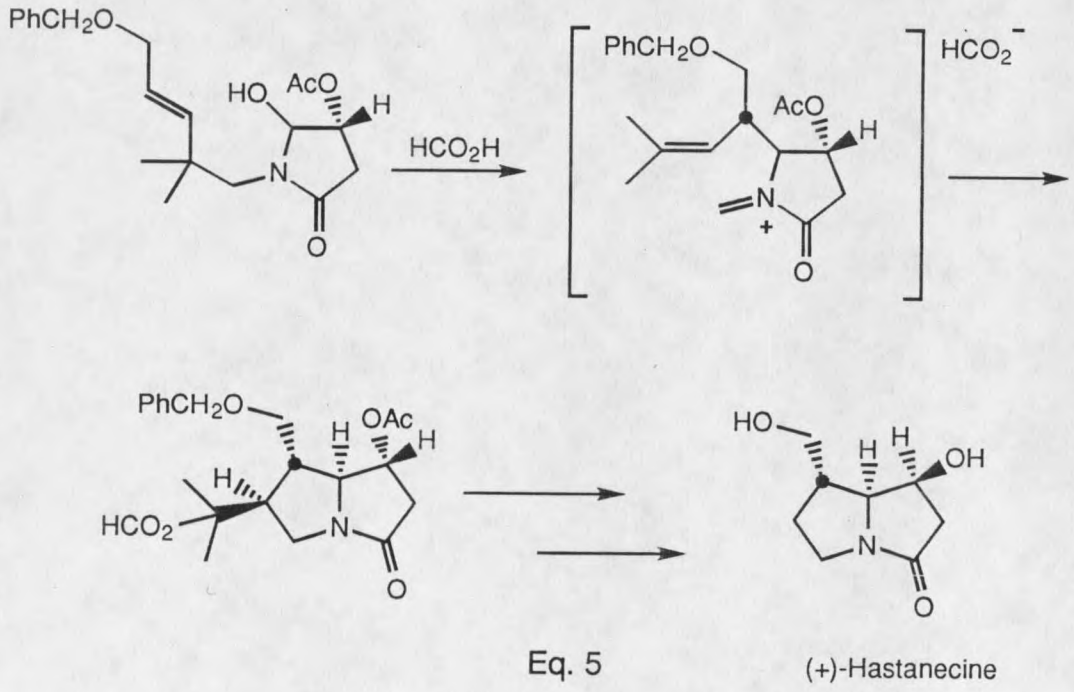
Scheme 4

An adaptation of the above work is the 2-aza-Cope *N*-acyliminium ion cyclization[8] where the active ring forming intermediate is obtained after an initial aza-Cope rearrangement takes place (Scheme 5). This method of cyclization

has been used frequently in the synthesis of natural products, as exemplified by Hart's synthesis of (-)-hastanecine[9] (Eq. 5).

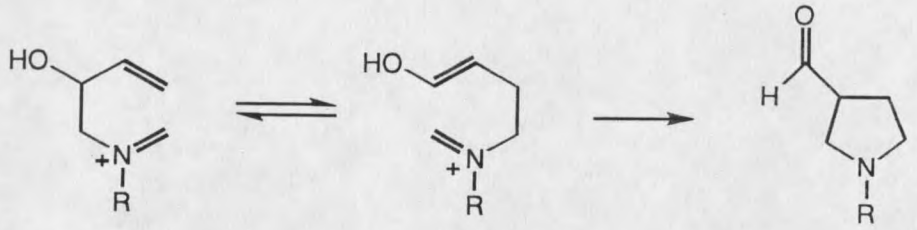


Scheme 5



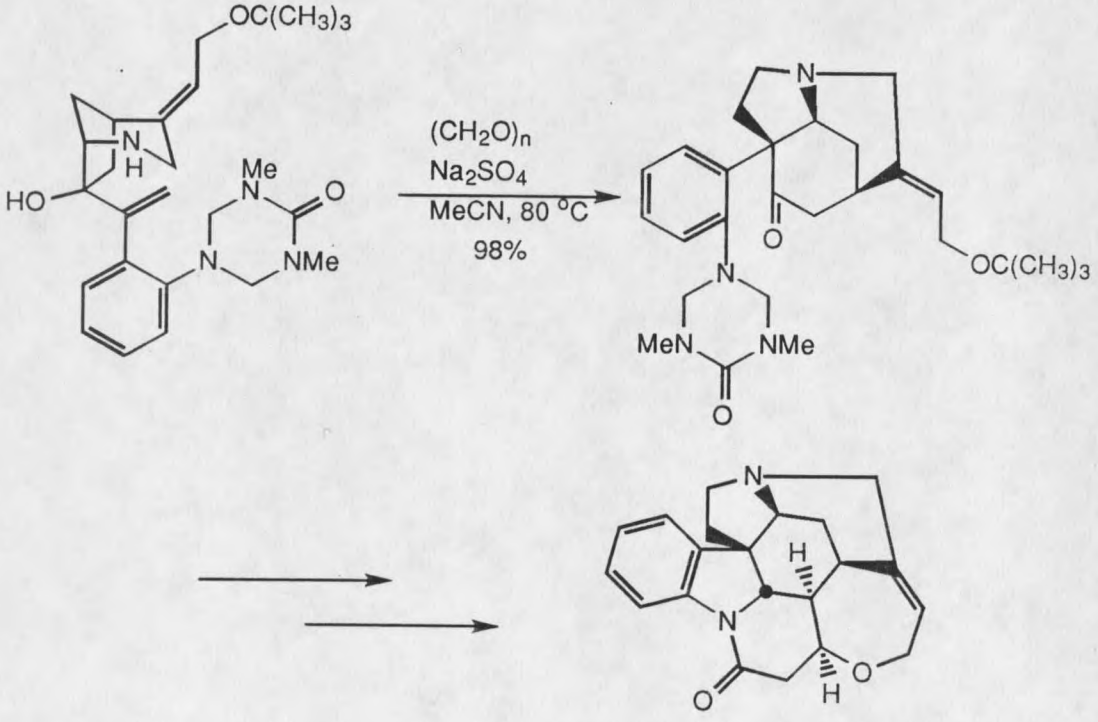
Eq. 5 (+)-Hastanecine

Another example of the utility of iminium ions in azacycle synthesis is the tandem aza-Cope-Mannich reaction (Eq. 6), developed by Overman,[10] which



Eq. 6

has also been of great utility in the synthesis of natural products. An example of this was demonstrated by the first enantioselective synthesis of (-)-strychnine[11] (Scheme 6). As with the related acyliminium ion reaction, the active cyclization

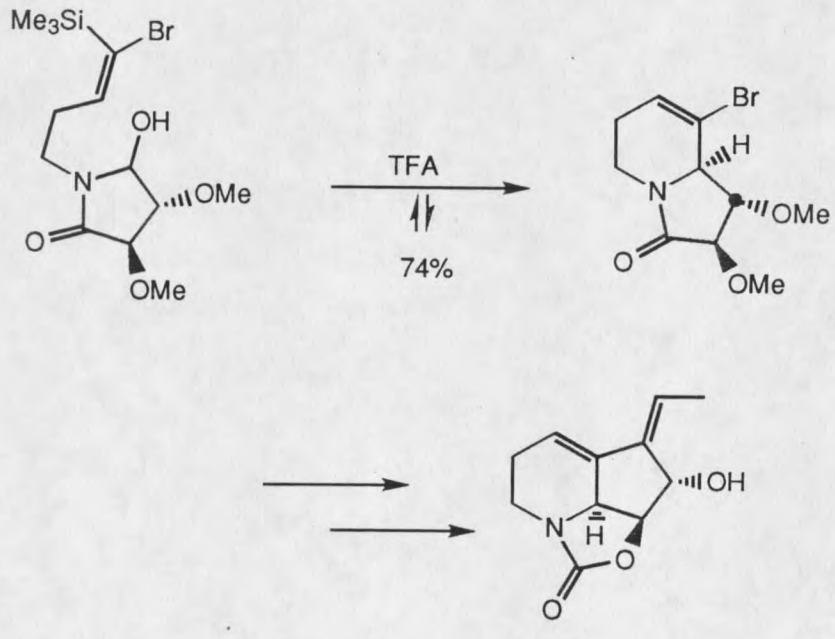


(-) - Strychnine

Scheme 6

intermediate is formed following an initial rearrangement. In this case, however, the intramolecular nucleophilic component is generated after the aza-Cope rearrangement as an enol. The ensuing Mannich cyclization is sufficiently exothermic that the initial [3,3]-sigmatropic rearrangement is rendered virtually irreversible.[12]

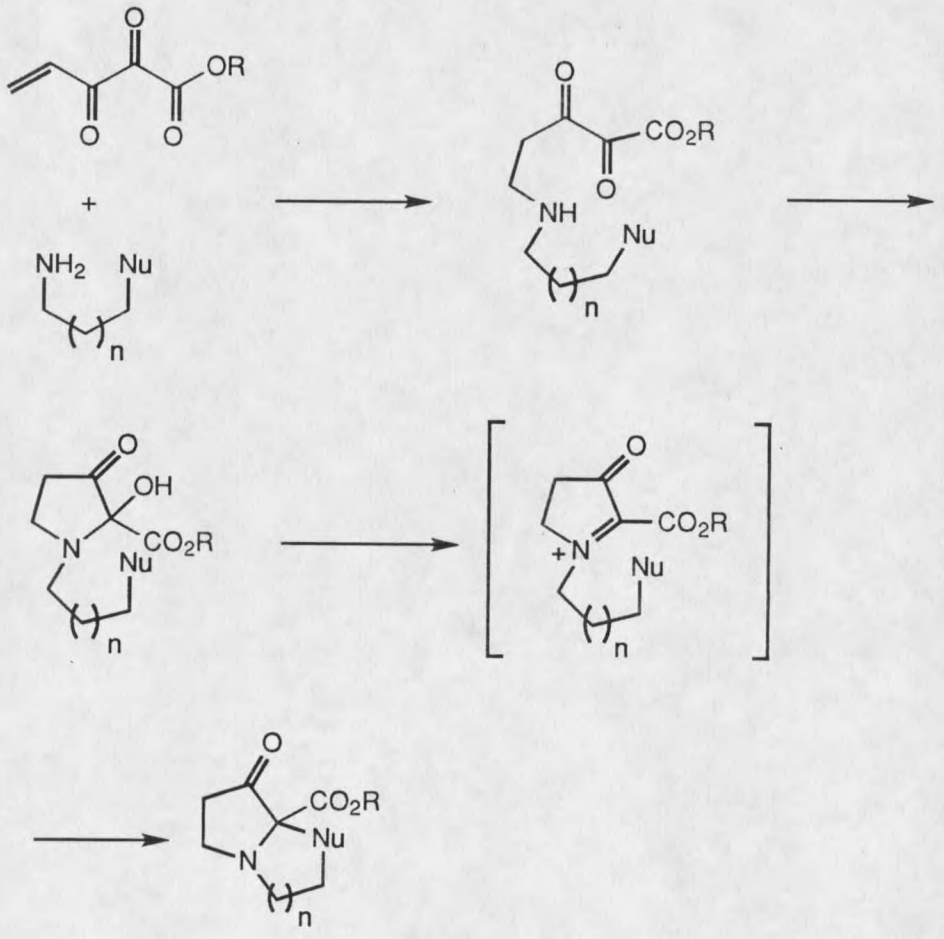
Other studies by Overman have shown that vinylsilanes act as excellent terminators of iminium and acyl iminium ion cyclizations. Due to the relatively mild conditions required for the generation of the reactive intermediate as well as termination, this methodology has been used with great success when applied to highly complex natural product syntheses, as illustrated by Overman's synthesis of (+)-streptazolin[13] (Scheme 7).



(+) - Streptazolin

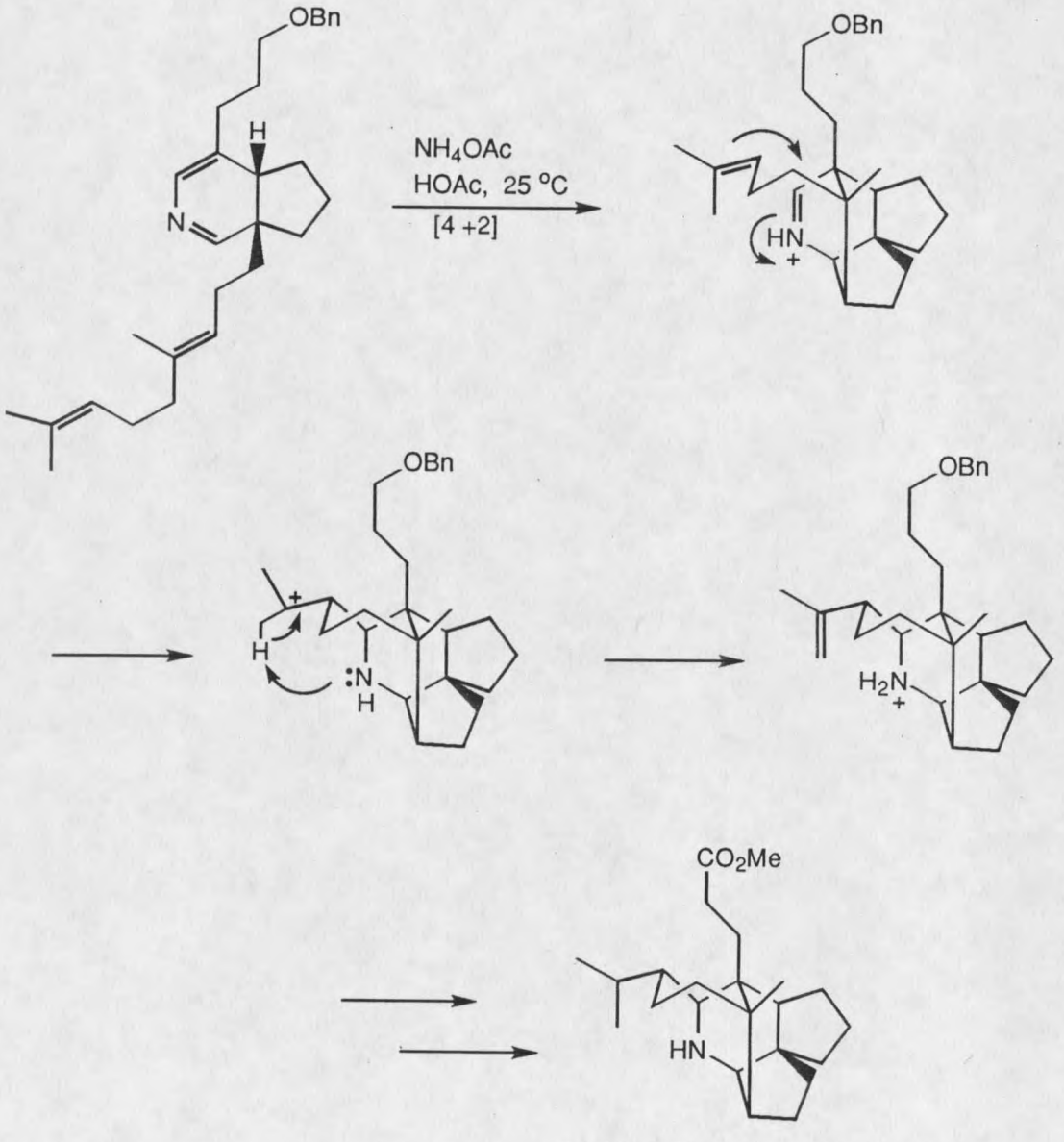
Scheme 7

A related intermediate that has recently been discovered is the *C*-acyliminium ion derived from vicinal tricarbonyls.[14] The highly electrophilic central carbon atom allows for cyclizations to take place when vinyl, propargyl, and allyl silanes are used as terminators. It has also been shown that aromatic rings, enol ethers, amide NH groups, and lactam NH groups can serve as nucleophiles in these cyclizations[15,16] (Eq. 7).



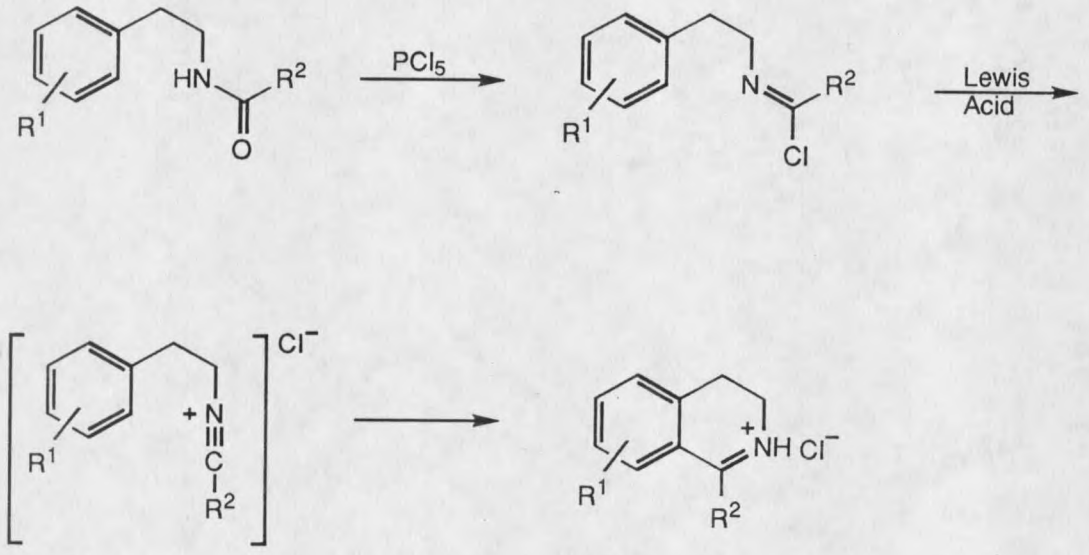
Eq. 7

Conjugated iminium ions have also been utilized as dienophiles in [4 + 2] cycloadditions. Heathcock[17] has recently demonstrated the usefulness of this type of reactive species in the synthesis of several *Daphniphyllum* alkaloids, an example of which is shown in Scheme 8.

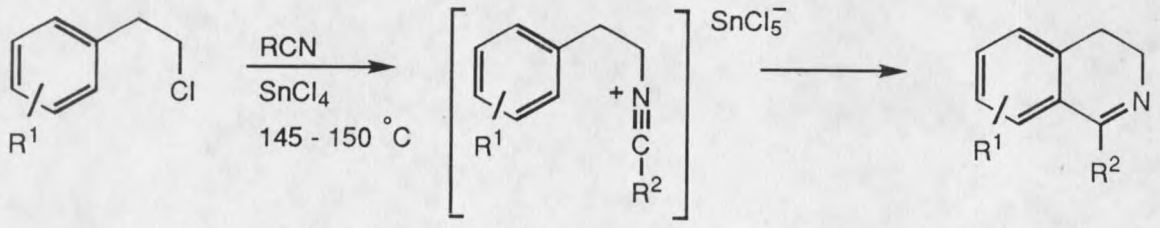


Scheme 8

Nitrilium ions are extremely reactive electrophilic intermediates that have been utilized for heteroannulations as well. Representative of these reactions are the Bischler-Napieralski reaction[18] (Eq. 8) and a method developed by Lora-Tamayo[19] (Eq. 9). However, both methods require strong Lewis Acids and high reaction temperatures which limit the usefulness of these reactions in the synthesis of molecules containing sensitive functional groups. To eliminate this problem in azacycle synthesis, a new method for nitrilium ion generation was sought by Livinghouse and coworkers.

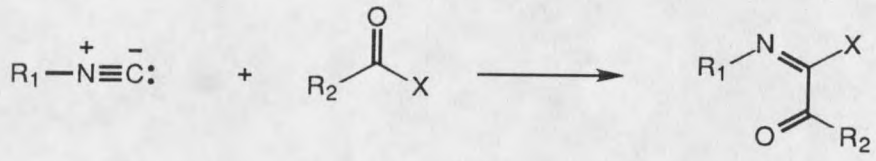


Eq. 8



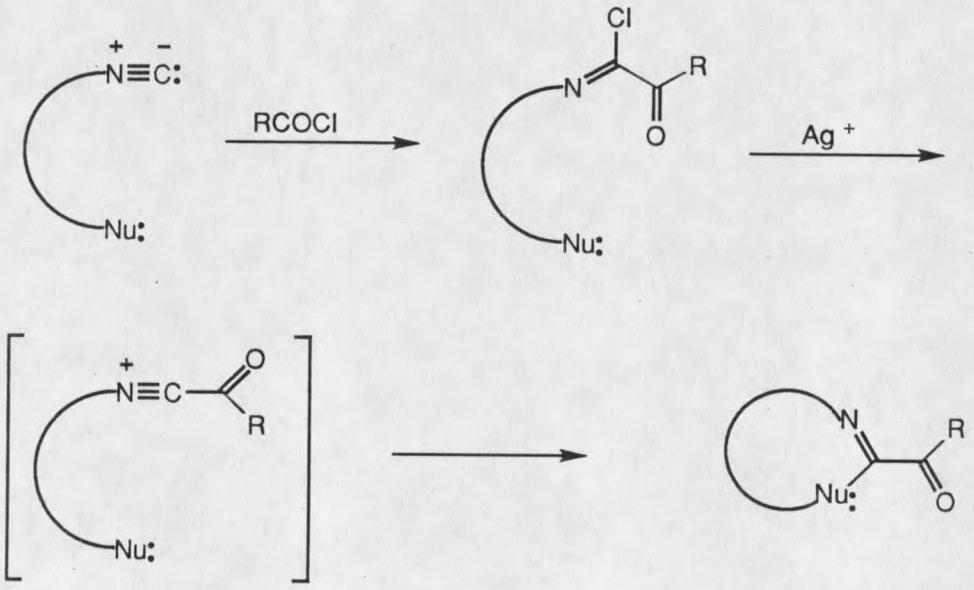
Eq. 9

The acylnitrilium ion intermediate had not previously been reported in the literature. However, in 1961 Ugi[20] reported the addition of acyl halides to isonitriles in good yields, resulting in stable α-ketoimidoyl halides (Eq. 10). It



Eq. 10

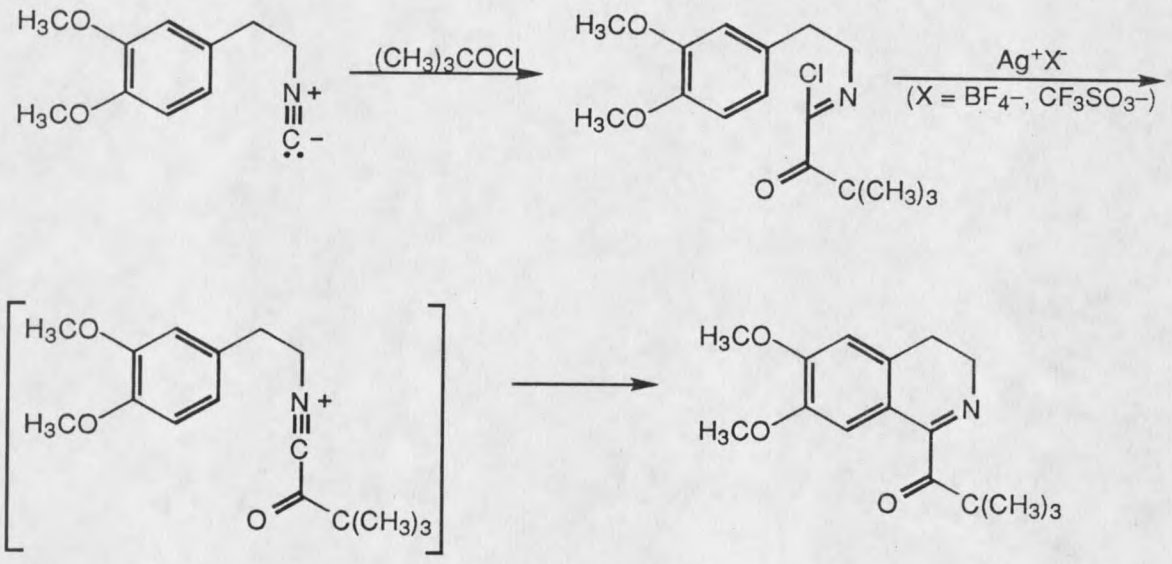
was believed by Livinghouse that upon treating this type of compound with a silver (I) salt, the halo-atom would be removed under mild conditions, resulting in the highly reactive *acyl*nitrilium ion (Eq. 11). It was thought that the cation



Eq. 11

could then be intercepted by simple nucleophiles such as arenes, similar to the Pictet-Spengler and Bischler-Napieralski reactions. Initial studies[21] to test this

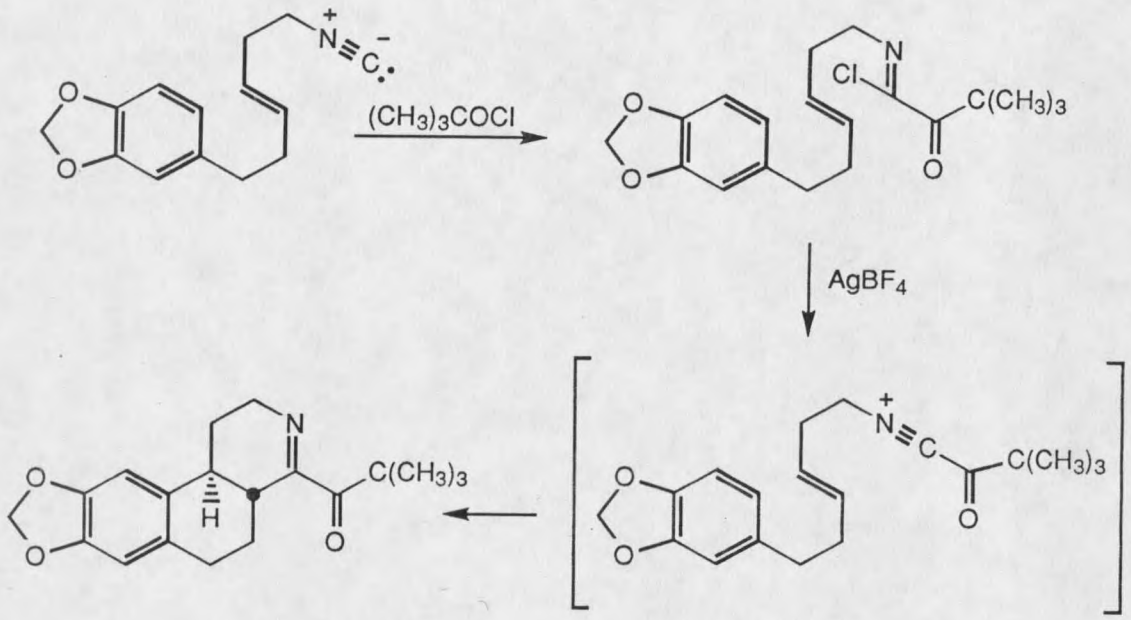
hypothesis found that the silver halide salt did indeed form, and the π-bond from an aromatic ring was sufficiently nucleophilic to add to the reactive component that was created (Eq. 12). Internal nucleophiles were then used to further



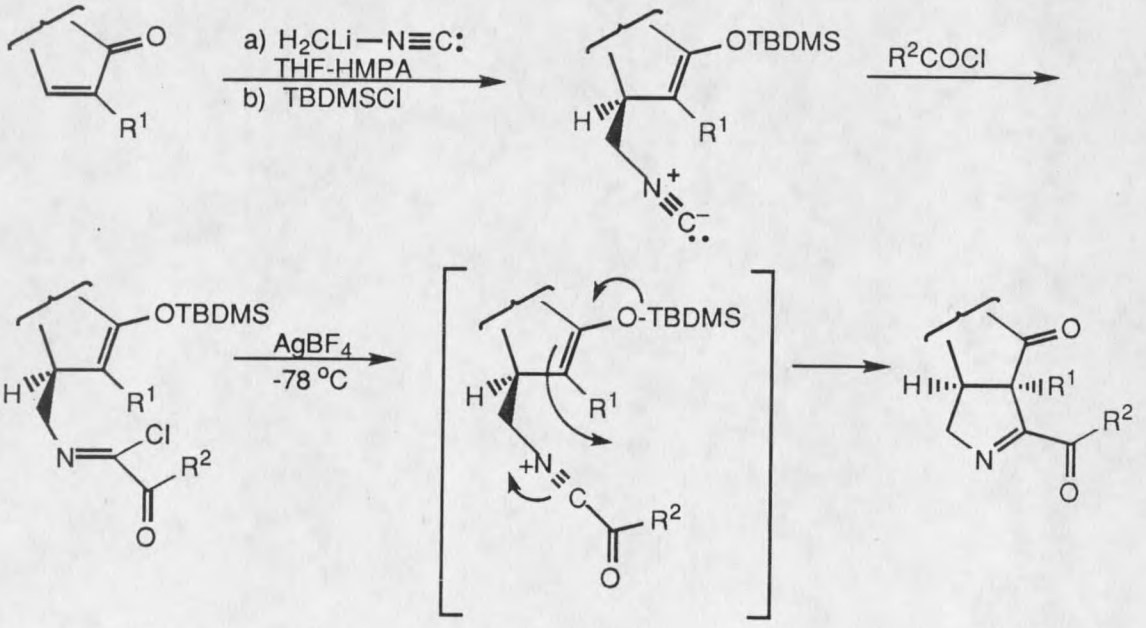
Eq. 12

study the generality of these acylnitrilium ion initiated annulations. As shown in Eq. 13, simple alkenes[22] can also be used for this purpose in a relay synthesis resulting in an extended ring system.

It was also predicted that silyl enol ethers[23] would act as excellent acylnitrilium ion-arene terminators. The 1,4-addition of $LiCH_2NC$: to α,β-unsaturated ketones, and trapping with *t*-butyldimethylchlorosilane gave 3-(isocyanomethyl)silyl enol ethers in high yields. Reaction of the isonitriles with the desired acyl chloride, followed by treatment with silver tetrafluoroborate, gave the expected Δ^1-pyrrolines in excellent yield (Scheme 9).

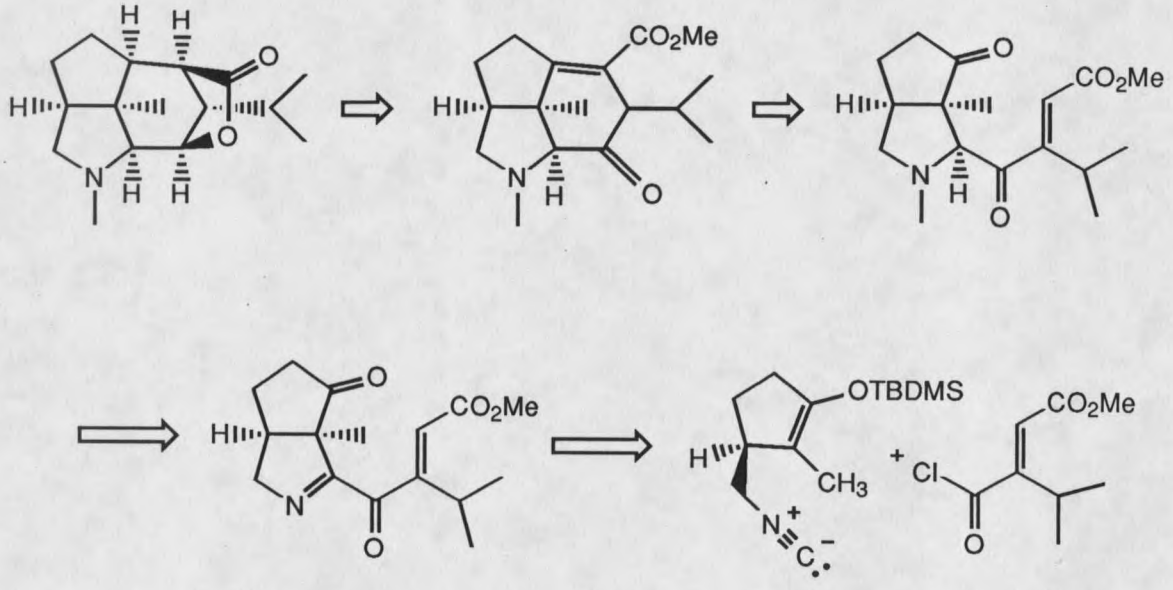


Eq. 13



Scheme 9

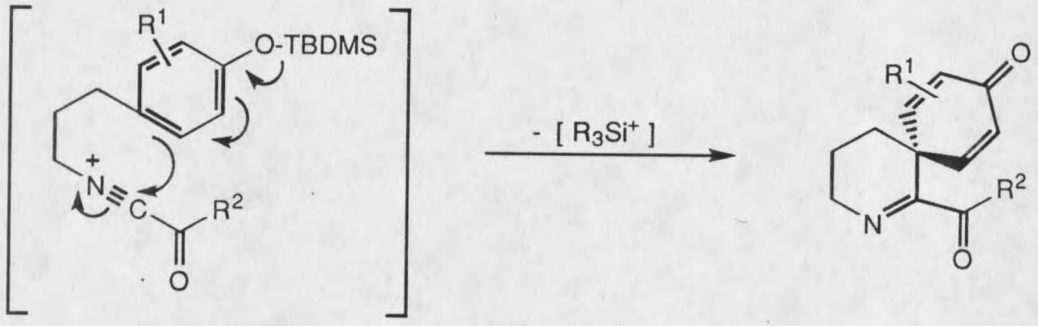
The utility of this methodology has been further demonstrated in these laboratories by its use in the total synthesis of the tetracyclic *Orchidaceae* alkaloid, dendrobine.[24] This efficient synthesis, consisting of eight linear steps, was carried out in 6.2 % overall yield with the key cyclization step as the highest yielding reaction (Scheme 10).



Scheme 10

These examples demonstrate that this method offers the advantage of a convergent assembly of azacycles of various ring sizes containing 2-acyl and endocyclic imine moieties, which can be utilized as sites for further functionalization. Most importantly, these cyclizations can be carried out under *extremely* mild conditions (-78 °C to -20 °C) and are therefore compatible with molecules containing other highly sensitive functionalities.

The focus of the research described herein was to expand upon the use of acylnitrilium ion initiated cyclizations and ascertain whether spirocyclizations could be accomplished utilizing phenolic silyl ethers as terminators (Scheme 11). Once this could be shown, the possibility existed of using this methodology in the total synthesis of the *Lycopodium* alkaloid serratine (**1**) (Figure 1).



Scheme 11

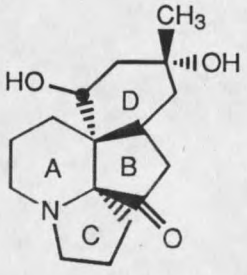


Figure 1. Serratine (**1**)

Nature of *Lycopodium* alkaloids

The *Lycopodium* alkaloids are unique in nature in that they are the only alkaloids found in club mosses. Of the 400 or so known varieties of club moss (genus *lycopodium*) only 10 % have been analyzed for alkaloid content.[25] From

these, over 100 different alkaloids have been isolated and are classified in 12 major skeletal systems shown in Figure 2.[26] One of the more recently discovered alkaloids, serratine (**1**), is found in *Lycopodium serratum* Thumb. and belongs to the minor serratinane skeletal group. This species has been

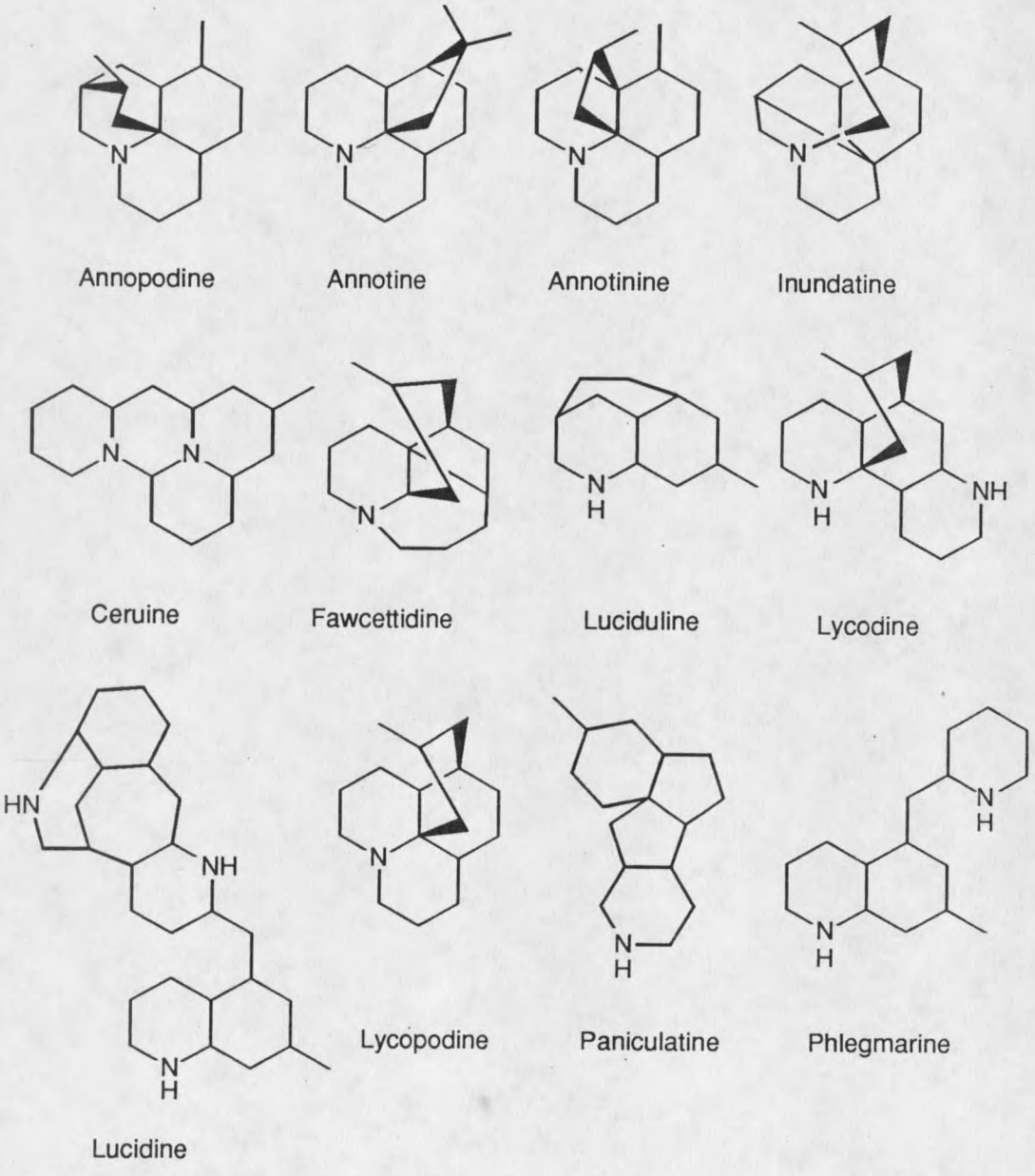


Figure 2. Major Skeletal Classes of *Lycopodium* Alkaloids

used in traditional Chinese herbal medicine due to its hemostatic and antipyretic activities.[27] Many other alkaloids are found in this species including lycololine, lycoclavine, serratinine, huperzine A, and huperzine B. The latter two compounds are currently being examined in China for the treatment of myasthenia gravis and Alzheimer's dementia[28] (Figure 3).

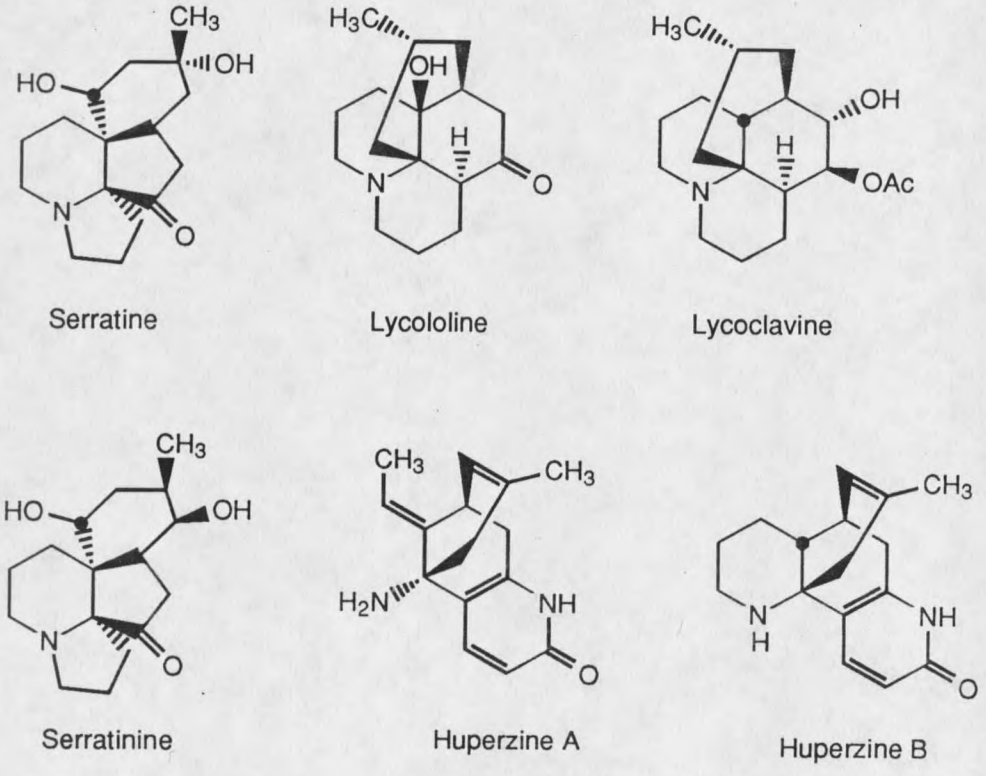
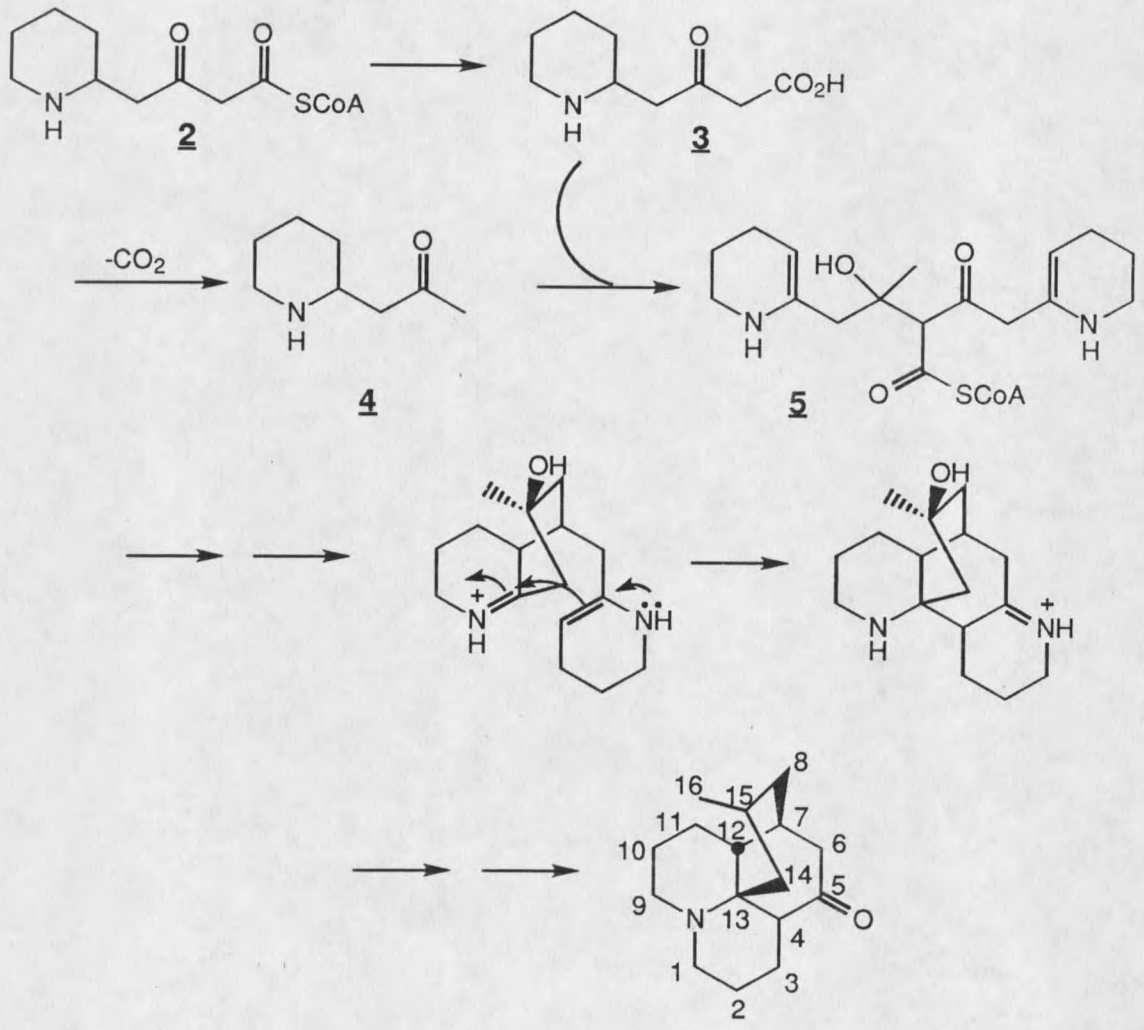


Figure 3. Representative Alkaloids within the Species *Lycopodium serratum* Thumb.

The biosynthesis of serratine most likely proceeds via a pathway common to the majority of the lycopodium alkaloids. A proposal for the biosynthesis of lycopodine has been put forth by Spencer and MacLean[29]

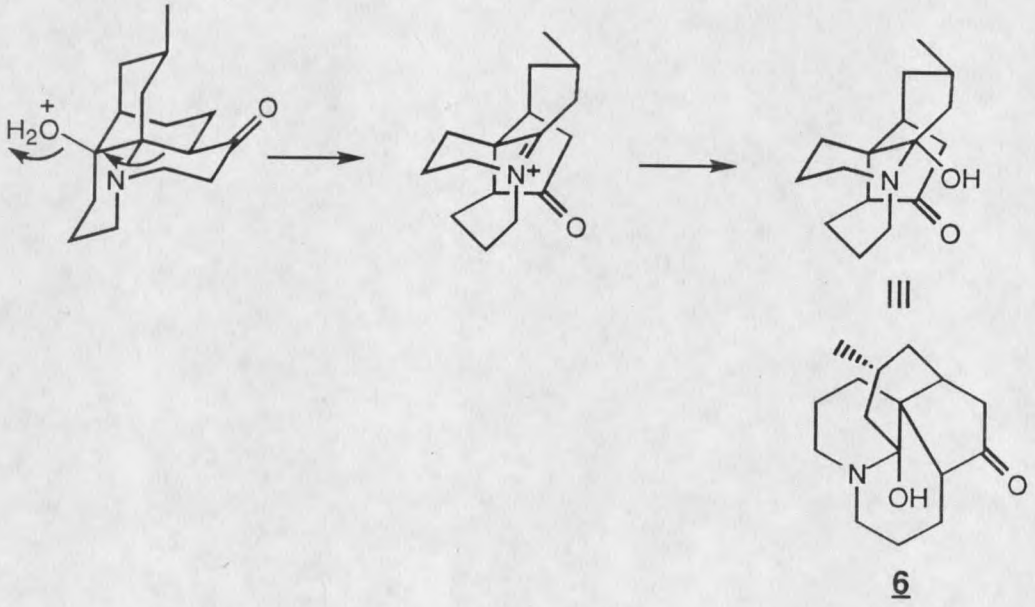
(Scheme 11). It suggests that lycopodine stems from the piperdine-2-acetoacetate derivative **2,** which in turn is derived from lysine. Decarboxylation



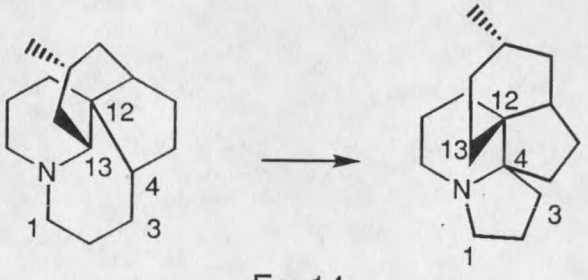
Scheme 11

of **3** would yield pelletierine **4**. Condensation of **4** with another molecule of **2** would produce **5**, the immediate precursor of the lycopodine alkaloids. Subsequent hydrolysis of the immonium salt and cyclization with the nitrogen contained in the A ring produces the lycopodine alkaloids.

A biosynthetic conversion between lycodoline (12-hydroxylycopodine) and fawcettimine (**6**) has been proposed by Inubushi[30] (Scheme 13). This is believed to be accomplished via protonation of the hydroxyl group, followed by loss of water, and then a migration of the C (4)-C (13) bond to yield the immonium salt, which upon hydration provides fawcettimine (**6**). The serratinane skeletal system is arrived at through one more bond migration, a Wagner-Meerwein shift of the C (13) - N bond to the C (4) position[31] (Eq. 14).



Scheme 13



Eq. 14

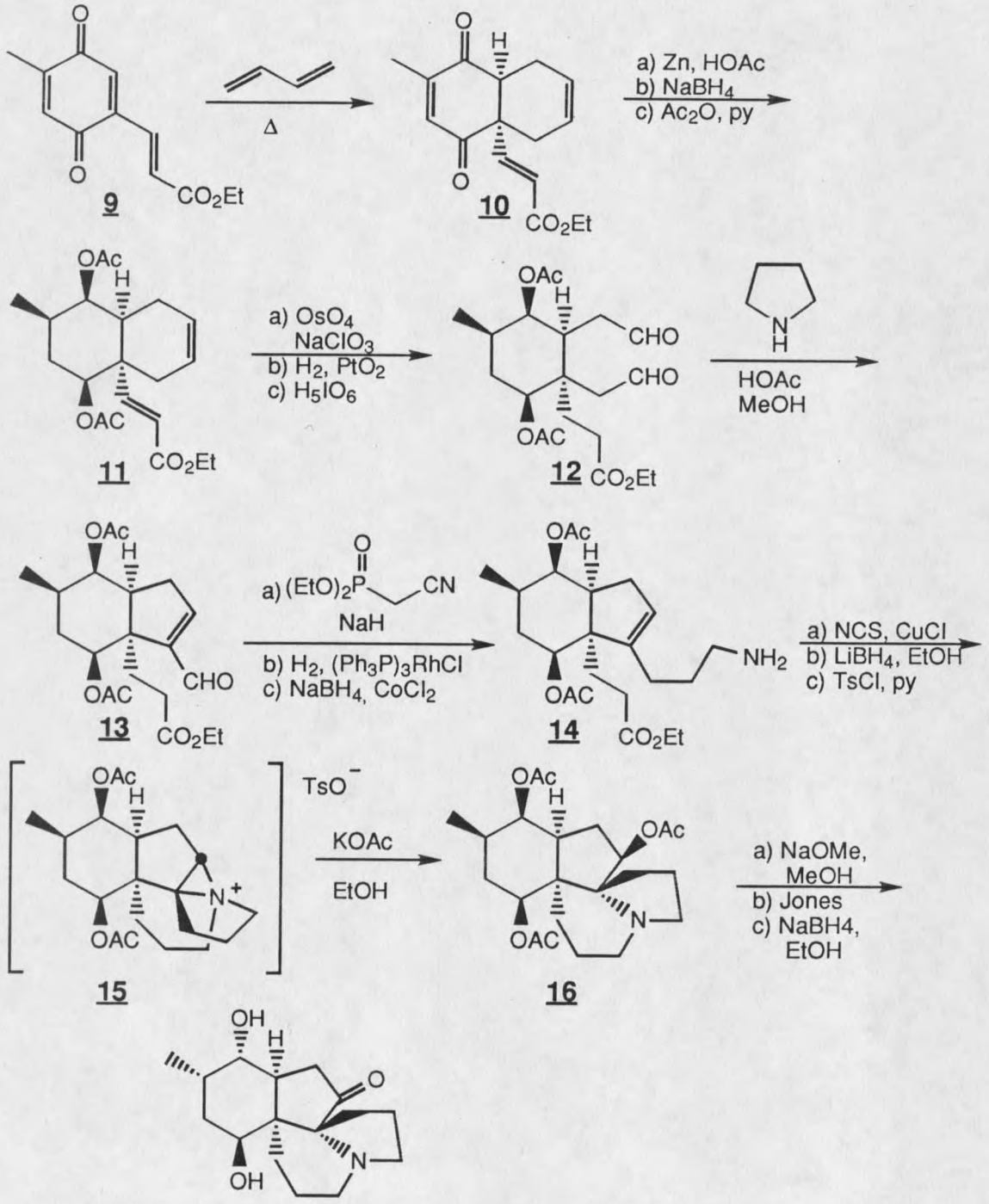
Previous Syntheses of *Lycopodium* Alkaloids with the Serratinane Skeleton

Many of the *Lycopodium* alkaloids have been synthesized. The most extensive synthetic studies have been performed on the most abundant alkaloid of the class, lycopodine. The initial routes to its skeleton were devised independently by Stork[32] and Ayer[33] in 1968. However, only two alkaloids of the serratinane group have been synthesized, (±)-serratinine (**7**)[34] and (±)-8-deoxyserratinine (**8**).[35] Both of these syntheses were carried out by Inubushi (Scheme 14 and Scheme 15).

The synthesis of (±)-serratinine (**7**) started with the benzoquinone **9**, which was heated with butadiene to yield the Diels-Alder product **10** in 39 % yield. The enedione system was reduced and then acylated to produce **11**. The isolated olefin was dihydroxylated upon treatment with osmium tetroxide, followed by hydrogenation of the remaining double bond. The resulting diol was cleaved with periodic acid to give the dialdehyde **12**. The use of Mannich conditions utilizing pyrrolidine and excess acetic acid in methanol resulted in a mixture of products, with the desired regioisomer **13** being favored in an 8 to 1 ratio. The aldehyde was then treated with diethyl cyanomethylphosphonate to yield the cinnamonitrile. The least substituted olefin and the cyano function were then reduced sequentially to furnish the amine **14**. In the following step, a nitrene was produced which adds to the double bond to yield the aziridine. The ester moiety was then reduced to yield the corresponding alcohol which was in turn tosylated, then displaced by nitrogen to produce the aziridinium salt **15**. Treatment of this salt with potassium acetate yielded triacetate **16**, containing

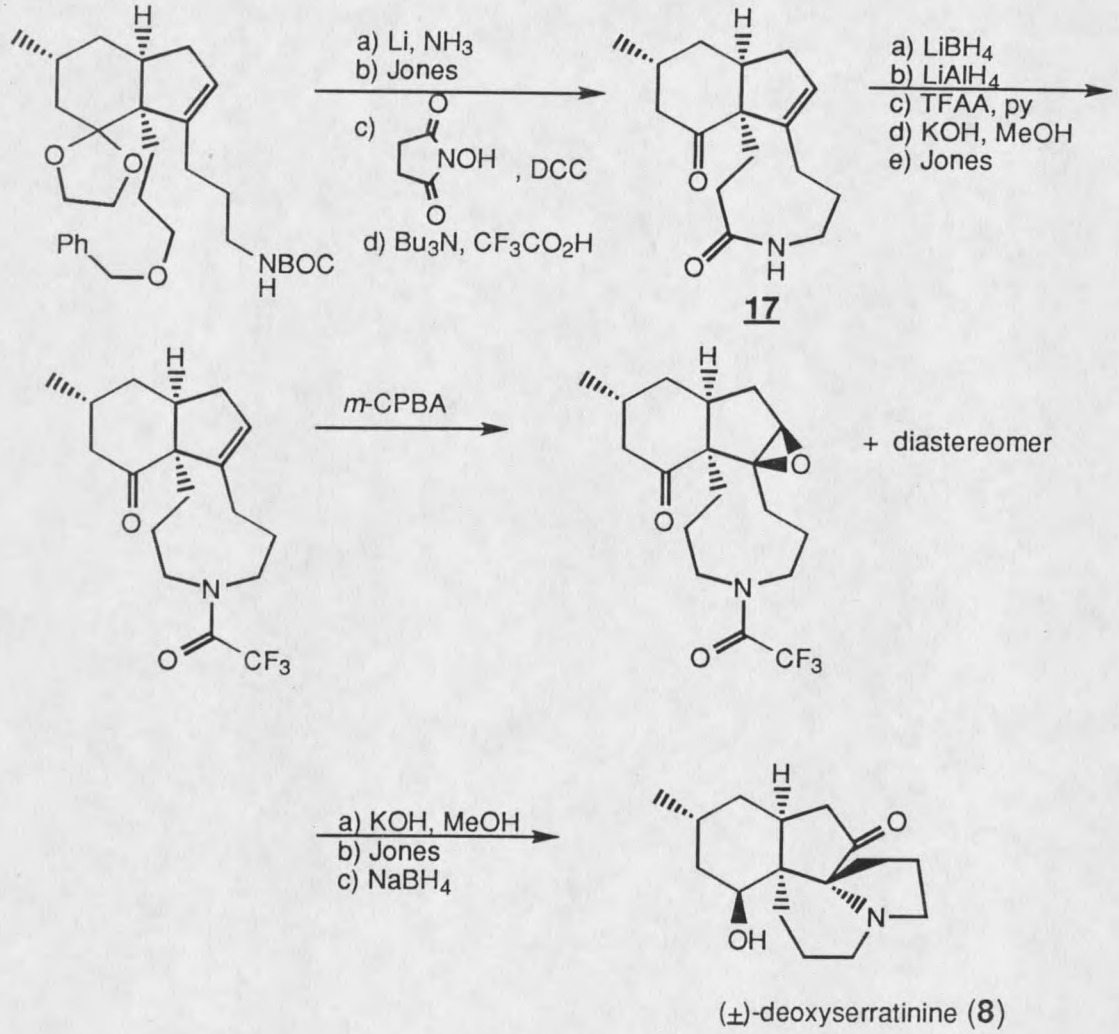
the serratinane ring skeleton. The synthesis was completed, following modifications of functional groups contained in this ring system, in an overall yield of less than 0.1 %.

The synthesis of (±)-8-deoxyderratinine (**8**) is similar to that of (±)-seratinine (**7**) except for the closure of the final two rings of the skeleton. This was accomplished by the formation of a nine-membered ring in **17**, which was followed by reduction of the amide and ketone. The resulting alcohol was then reoxidized and the amine protected with a triflouroacetyl moiety. *m*-CPBA was then employed to epoxidize the olefin. Upon generation of the amine, the tetracyclic alcohol was produced in quantitative yield. Following oxidation of the alcohol and selective reduction of the less hindered ketone, the target molecule **8** was obtained. This synthesis was also accomplished in less than 0.1 % overall yield.



(±)-Serratinine (**7**)

Scheme 14

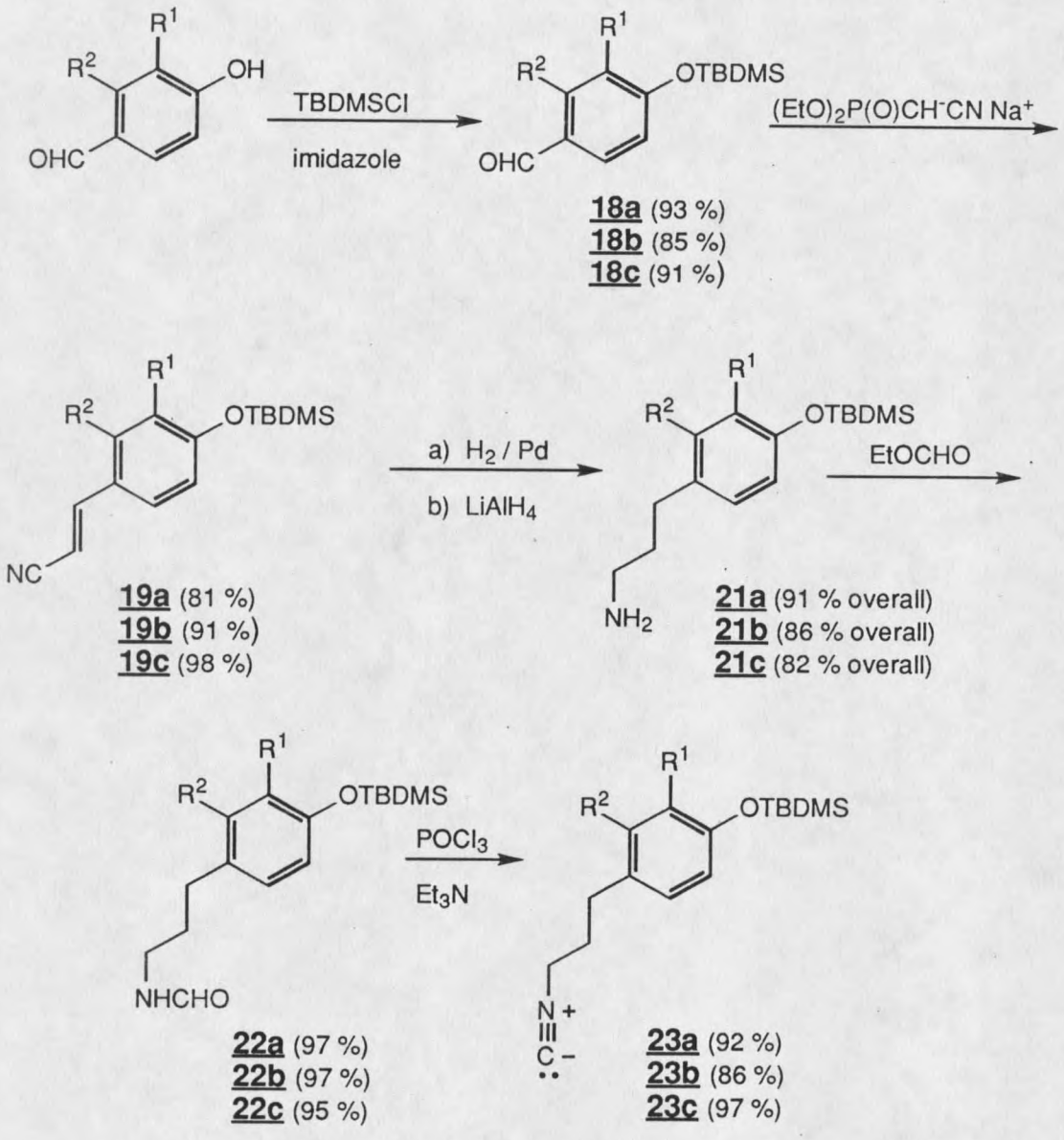

a) Li, NH3
b) Jones
c)
NOH
, DCC
d) Bu3N, CF3CO2H
a) LiBH4
b) LiAlH4
c) TFAA, py
d) KOH, MeOH
e) Jones
17
m-CPBA
+ diastereomer
a) KOH, MeOH
b) Jones
c) NaBH4
(±)-deoxyserratinine (8)

Scheme 15

RESULTS AND DISCUSSION

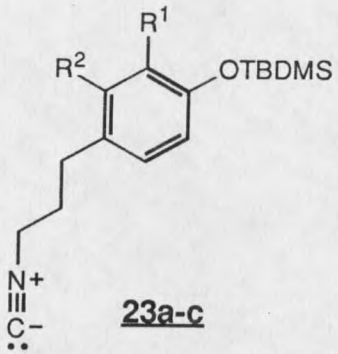
Methods Development

The aim of this research was to determine the feasability of using phenolic silyl ethers as terminators in acylnitrilium ion-arene spiroannulation reactions (Scheme 11). As seen in Scheme 16, the requisite isonitriles were synthesized by first silylating the phenols,[36] whereupon the Horner-Wadsworth-Emmons reagent[37] was employed to produce the cinnamonitriles **19a-c**. This was followed by hydrogenation of the olefins, reduction of the nitriles, and formylation of the resulting amines **21a-c**. The formamides **22a-c** were then dehydrated, giving rise to the respective isonitriles **23a-c**. Each isonitrile was subsequently treated with trimethylacetylchloride (25 °C) in $CDCl_3$ and the reaction monitored to completion by NMR. This was followed by addition to $AgBF_4$ in a solution of dichloromethane and 1,2-dichloroethane (-78 °C to -20 °C), which resulted in the spirocyclic products in the case of **23a** and **23b** (Scheme 17). However, in the case of **23c**, the 7-membered ring adduct was formed. This result was in congruence with what was found using the piperonal derived isonitrile **23d** (Eq. 15), formed by treating piperinal **26** with KOH in acetonitrile[38] to give the corresponding cinnamonitrile **19d** (Eq. 16), and then following the same series of steps taken for **19a-c**.



(**a:** $R^1 = R^2 = H$; **b:** $R^1 = H$, $R^2 = OCH_3$; **c:** $R^1 = OCH_3$, $R^2 = H$)

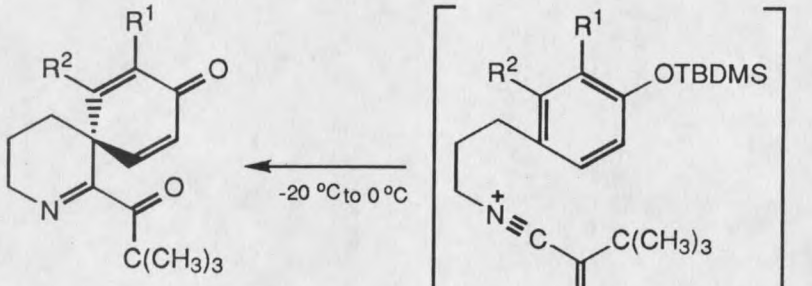
Scheme 16



23a-c

(**a:** $R^1 = R^2 = H$; **b:** $R^1 = H$, $R^2 = OCH_3$; **c:** $R^1 = OCH_3$, $R^2 = H$)

a) $(CH_3)_3CCOCl$, 25 °C, $CDCl_3$ | b) $AgBF_4$, -78 °C, 1,2-DCE-CH_2Cl_2

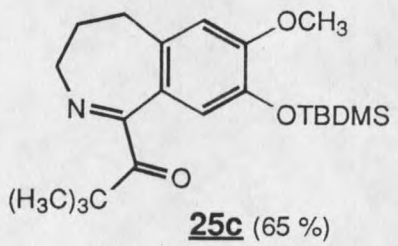


-20 °C to 0 °C

25a: $R^1 = H$, $R^2 = H$ (70 %)

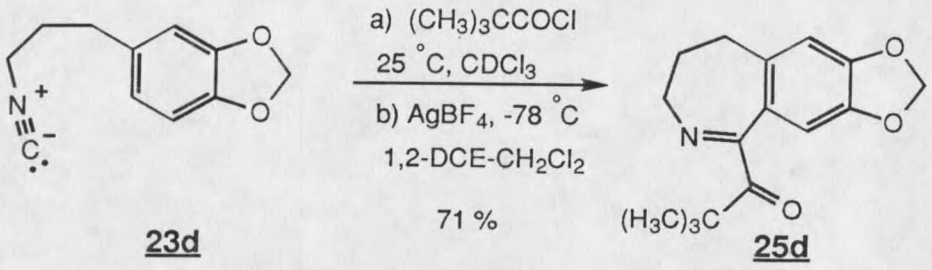
25b: $R^1 = H$, $R^2 = OCH_3$ (82 %)

-20 °C

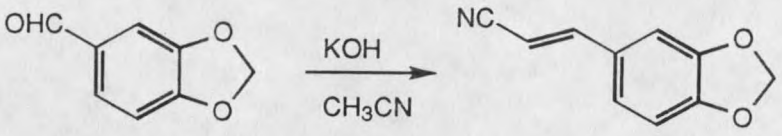


25c (65 %)

Scheme 17



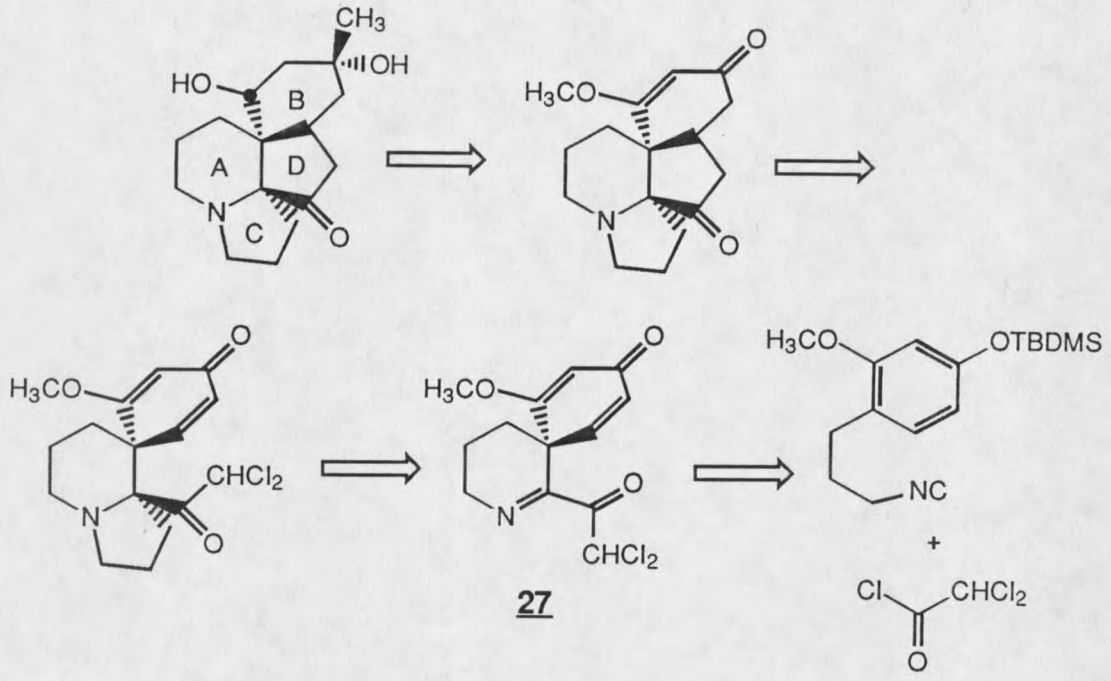
Eq. 15



Eq. 16

StudiesToward the Synthesis of Serratine

Fortunately, it was determined that the desired spirocyclic precursor required for the synthesis of serratine (**1**) could be formed utilizing our acylnitrilium ion methodology. It was hoped that from spirocycle **27**, the tetracyclic core structure of serratine could be formed in the manner shown in Scheme 18.

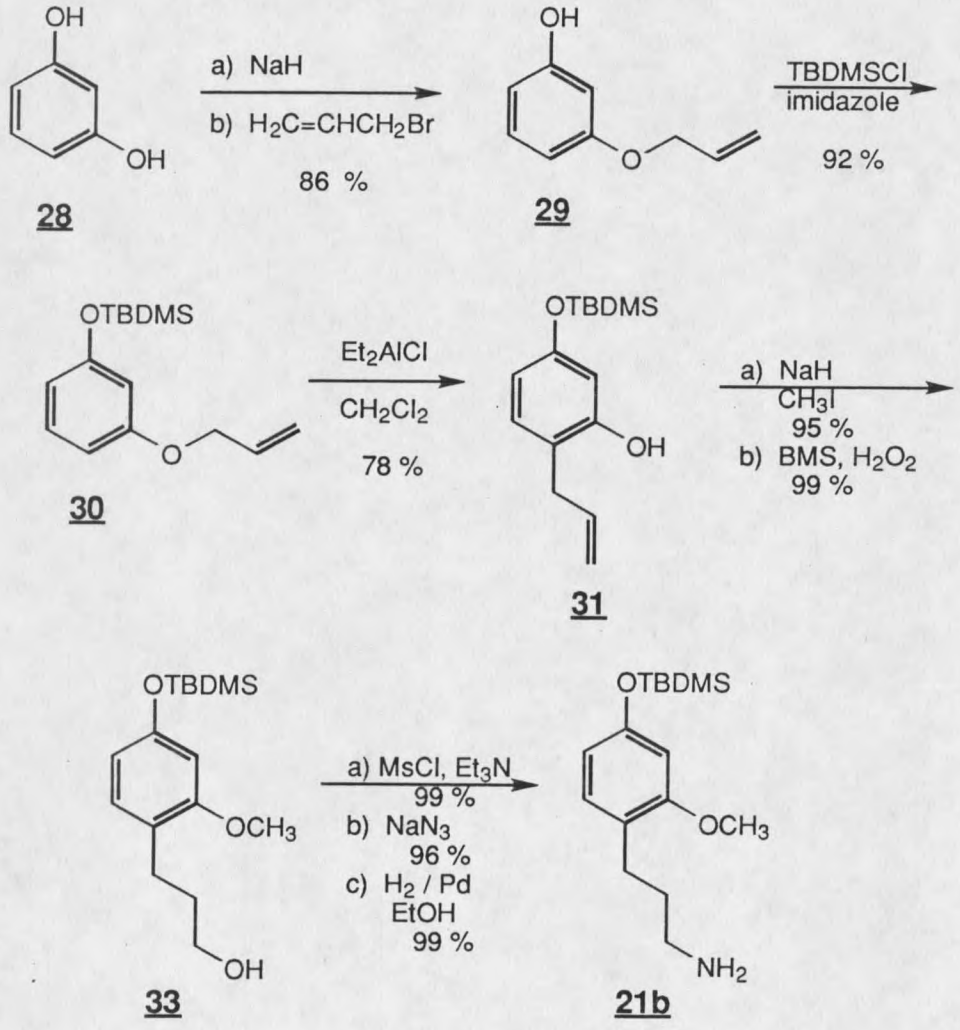


Scheme 18

Upon formation of the spirocycle, it was hoped that the imine contained within the molecule could be functionalized in a manner that would yield closure of the C ring. We then believed that it would be possible to form the D ring utilizing the dichloroacyl moiety in a radical ring closure following known procedures.[39] All that would remain to complete the total synthesis would be modification of the functionality embedded within this tetracyclic core.

Before proceeding with the synthesis toward the natural product, a new pathway to the required isonitrile needed to be developed. The reasons for this were two-fold, first the cost of commercial 4-hydroxy-2-methoxybenzaldehyde used in the initial studies was exceedingly high, and second, if it was found nessessary to place a different substituent on the 3-position of the aromatic ring later in the synthesis, it seemed prudent that it should be done at an early stage

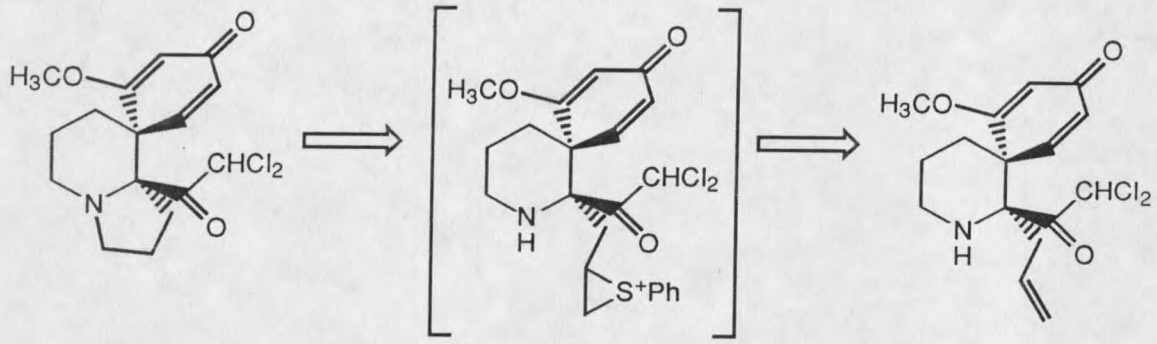
of the synthesis. This was accomplished as shown in Scheme 19. Resorcinol **28** was monofunctionalized through treatment with one equivalent of NaH followed by alkylation with allyl bromide (0.75 equiv.). The resulting phenol was



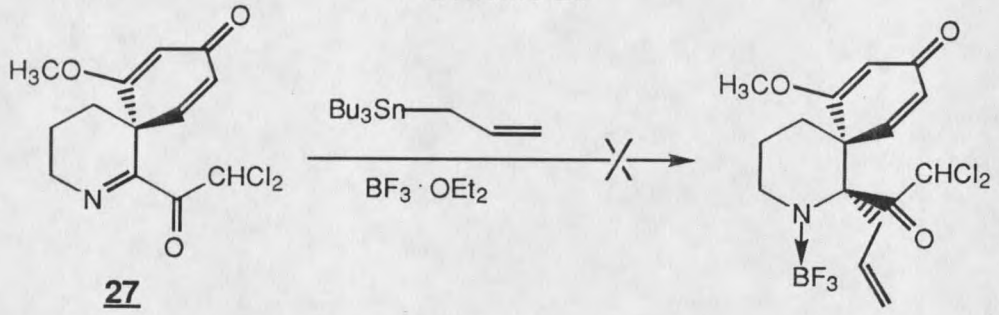
Scheme 19

protected with *t*-butlydimethylsilylchloride.[36] *Para* functionalization of this protected phenol was realized through a diethylaluminum chloride catalyzed Claisen rearrangement.[40] It should be noted that if the reaction temperature exceeded -30 °C, considerable amounts of product with undesired *ortho* substitution were obtained. The methoxy derivative was prepared by treatment with NaH and iodomethane in THF. Hydroboration of the olefin with borane-methyl sufide complex, followed by oxidative workup afforded the alcohol in excellent yield. Preparation of the mesylate was accomplished by treating the alcohol with MsCl and Et_3N in CH_2Cl_2. Displacement of the mesylate with sodium azide in DMF yielded the corresponding azide. Subsequently, the amine was obtained via hydrogenation of the azide in nearly quantitative yield. The remaining two steps to the isonitrile were performed as previously described.

As mentioned, the spirocycle **27** was to be the initial substrate utilized, as it was believed that the dichloroacyl group could ultimately be used to form the B ring of the system. With this in mind, attempts were made to functionalize the imine contained within the A ring. The first method employed was to treat the spirocycle with boron trifluoride diethyl etherate and allyltributyltin, which was hoped to yield the secondary amine. Following the precedent by Ishibashi, utilizing known episulfonium ion methodology,[41] it was believed that the C ring could be secured (Scheme 20). However, much to our concern, no reaction was observed (Eq. 17).



Scheme 20



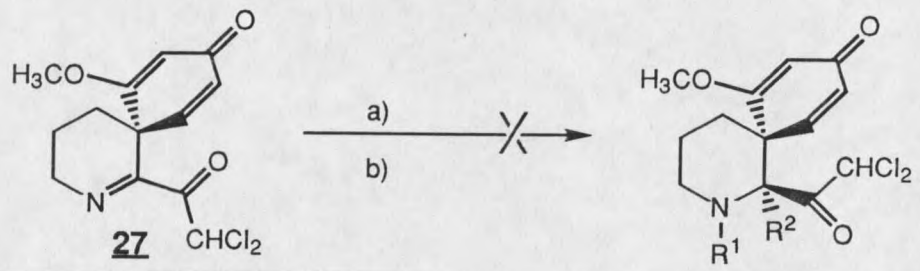
27

Eq. 17

We then sought to increase the electrophilicity of the imine carbon by creating the corresponding iminium ion, formed for the initial investigation by treating **28** with methyl triflate in CH_2Cl_2 or $CDCl_3$. As shown in Table 1 many different nucleophiles were utilized but none were successful.

Allyl tributyltin was also used on the iminium ion derived from MEM-Cl, MOM-Br, and also on the *N*-acyliminium ion derived from treatment of the spirocycle with trifluoromethylacetyltriflate (TFAT). None of these attempts were successful either. It was then realized that perhaps intramolecular functionalization methods, stemming from the initial alkylation of the imine, would be required due to steric constraints.

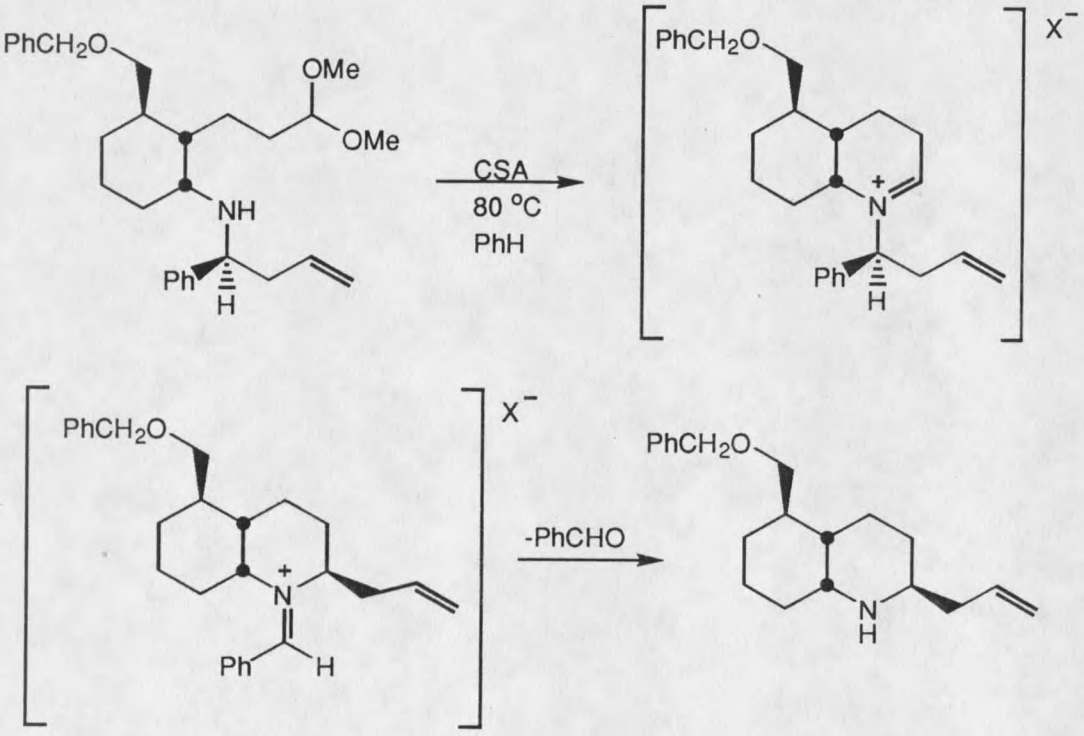
Table 1. Unsuccessful Attempts to Functionalize Spirocycle **27**



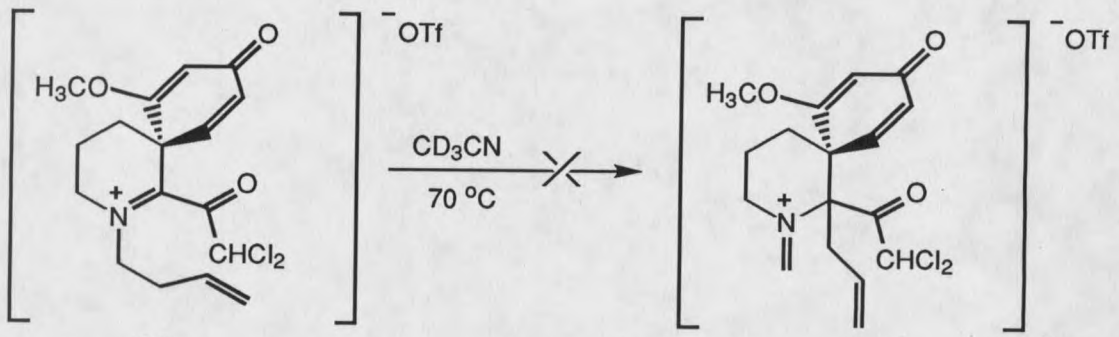
Trial	Reagents
1	a) CH_3OTf b) Bu_3Sn
2	a) CH_3OTf b) Bu_3Sn , $BF_3 \cdot Et_2O$
3	a) CH_3OTf b) Bu_3Sn , $SnCl_4$
4	a) CH_3OTf b) Me_3Si
5	a) CH_3OTf b) BuCu(CN)Li
6	a) CH_3OTf b) BrZn CuCN / 2 LiCl
7	a) CH_3OTf b) TMSCN
8	a) CH_3OTf b) *n*-BuCuCN(Mg)Br
9	a) MEM-Cl b) Bu_3Sn
10	a) MOM-Br b) Bu_3Sn
11	a) TFAT b) Bu_3Sn

Our initial strategy for intramolecular functionalization of the imine was to use an aza-Cope rearrangement, previously demonstrated to be effective by Overman[42] (Eq. 18). The triflate salt **36** was prepared cleanly upon treatment of the spirocycle with the corresponding alkyl triflate. The subsequent reaction was monitored by NMR in CD_3CN but again no addition to the iminium ion was seen even after extended periods at 75 °C (Eq. 19).

The second strategy was based on similar work by Macdonald[43] in which an *N*-acyliminium ion was formed in situ upon treatment of a hydroxylactam with $TiCl_4$. This reactive species was attacked by the nucleophilic carbon adjacent to a trimethyltin moiety (Eq. 20).

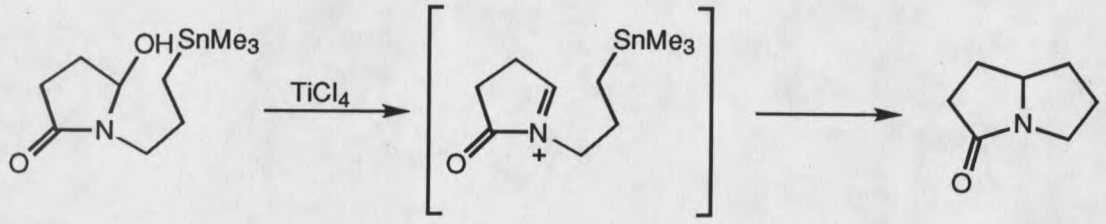


Eq. 18



36

Eq. 19

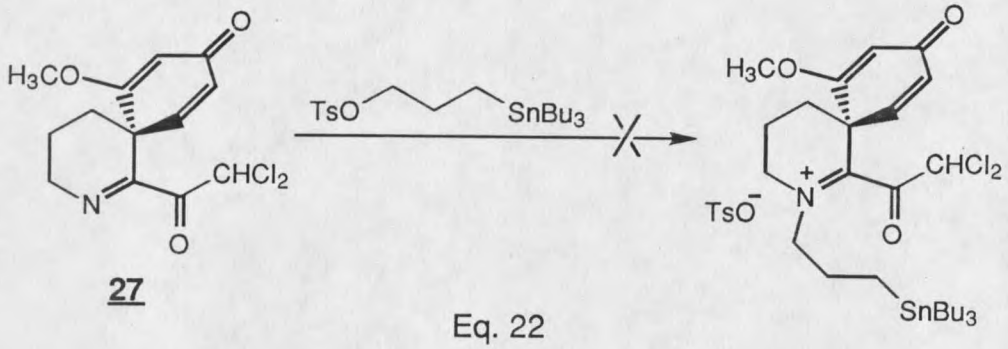


Eq. 20

Knowing that it was possible to cleanly alkylate the spirocycle with triflates, an endeavor was made to form a reagent containing both the required triflate and tributlytin moiety from the corresponding alcohol.[44] However, upon its generation, the nucleophilicity of the tributylorganostannane was clearly demonstrated as cyclopropane was believed to be immediately generated, as evidenced by escaping gas and the recovery of tributyltin triflate (Eq. 21). The tosylate derivative was formed in expectation that it would serve as an adequate leaving group in the alkylation of the imine, but it was found to be ineffective (Eq. 22) The same result was observed with the acid bromide derivative[45] (Eq. 23).

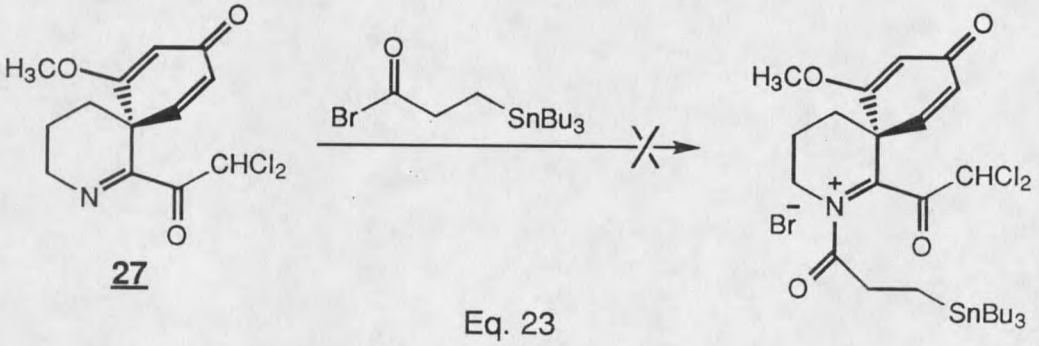


Eq. 21



27

Eq. 22

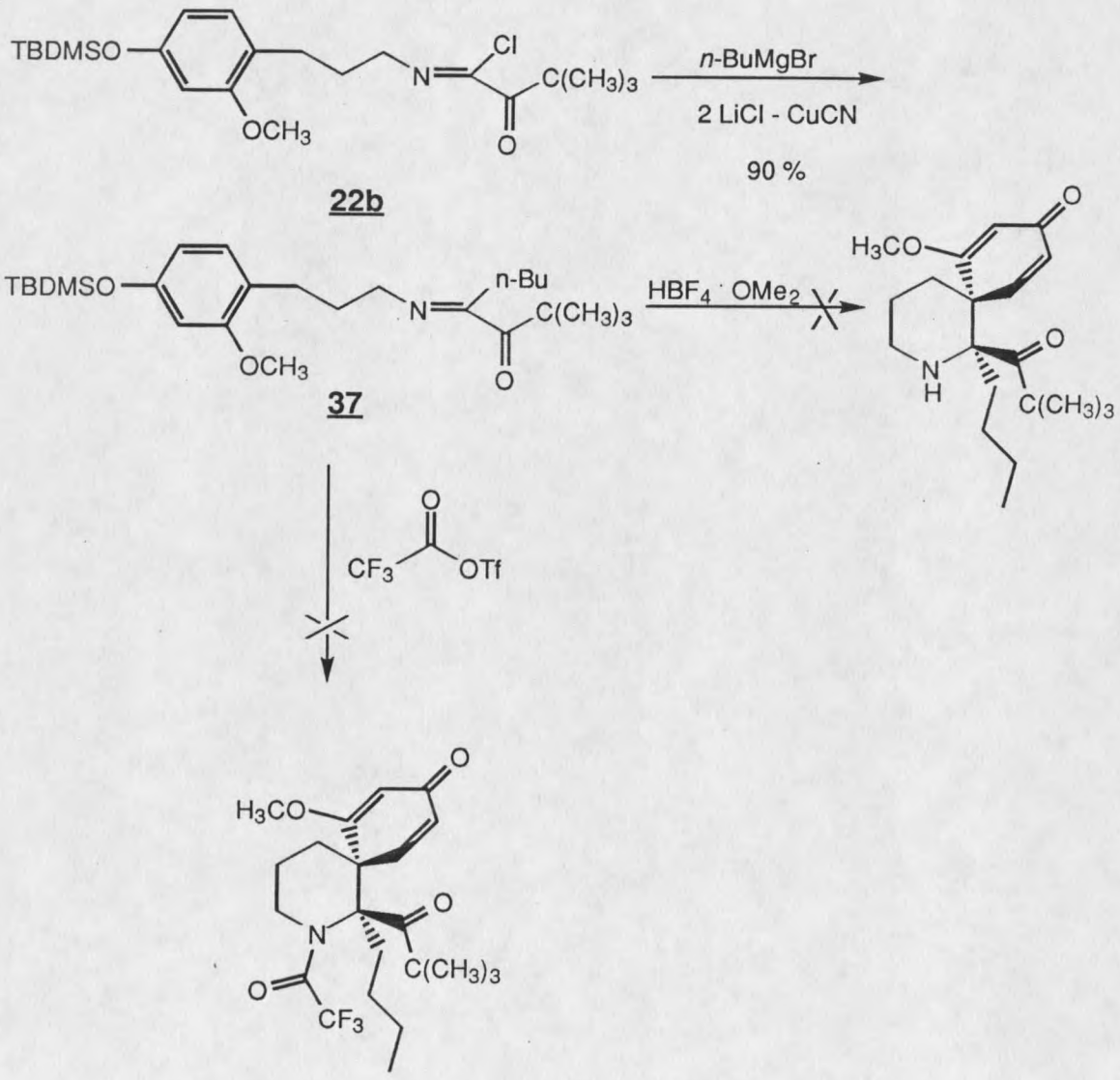


27

Eq. 23

At this point, the difficulty in forming a quaternary center adjacent to a preexisting quaternary center was becoming quite apparent due to the severe steric congestion at that site. The use of the extremely electrophilic *C*-acylnitrilium ion as the cyclization initiator was abandoned briefly in hopes that

a *C*-acyliminium ion could be substituted and thereby form the two adjacent quaternary centers in the initial ring forming step (Scheme 21). The required

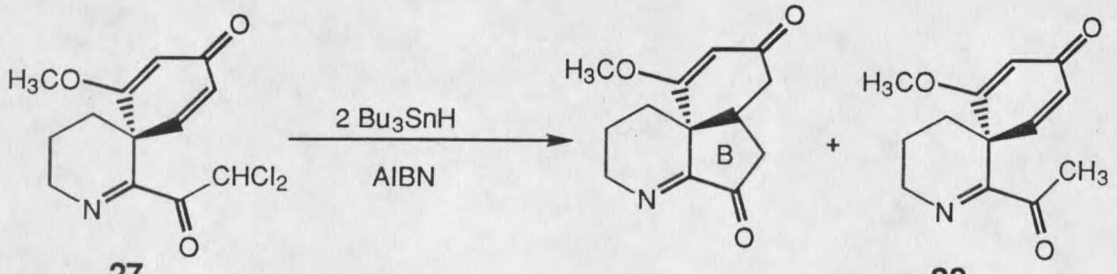


Scheme 21

imine **37** was formed by treating the α-ketoimidoyl chloride **22b** with a lower order cyanocuprate. This compound was then treated with $HBF_4 \cdot OMe_2$ with the

hope that this reagent could form the iminium ion and serve as a deprotection agent, thus driving the cyclization to the desired product . However this idea did not come to fruition. The imine was also treated with trifluoroacetyltriflate in the same vein but once again no reaction was observed.

Bearing all of these negative results in mind, attention was turned to the formation of the B ring of the molecule. It was hoped that once this was formed, it would relieve some of the steric constraints of nucleophilic addition to the imine and perhaps at the same time change the electronic characteristics of this section of the molecule, making addition to the imine favorable. We then proceeded with the next step in our initial synthetic plan for this ring formation, however, it was soon discovered that these plans were flawed in that the desired radical cyclization did not occur, only reduction product was formed under the conditions used by Ishibashi[39] (Eq. 24). Further studies on this type

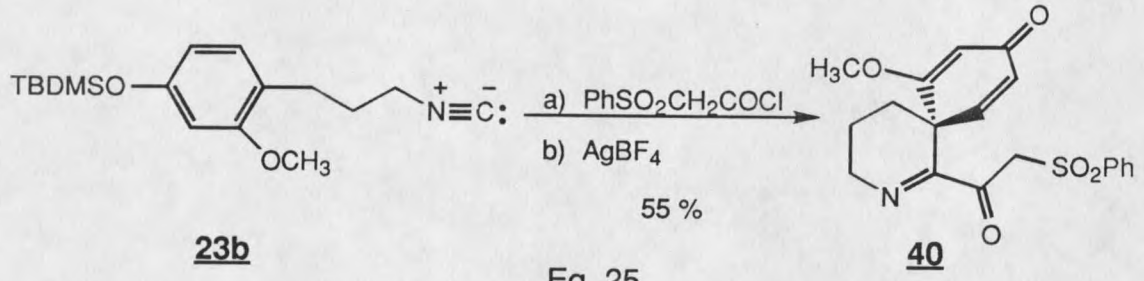


Eq. 24

of ring closure were not carried out, instead, attempts to form the ring using conjugate addition methodology[46] were examined with the hope that the additional functionality required would come into service later in the synthesis.

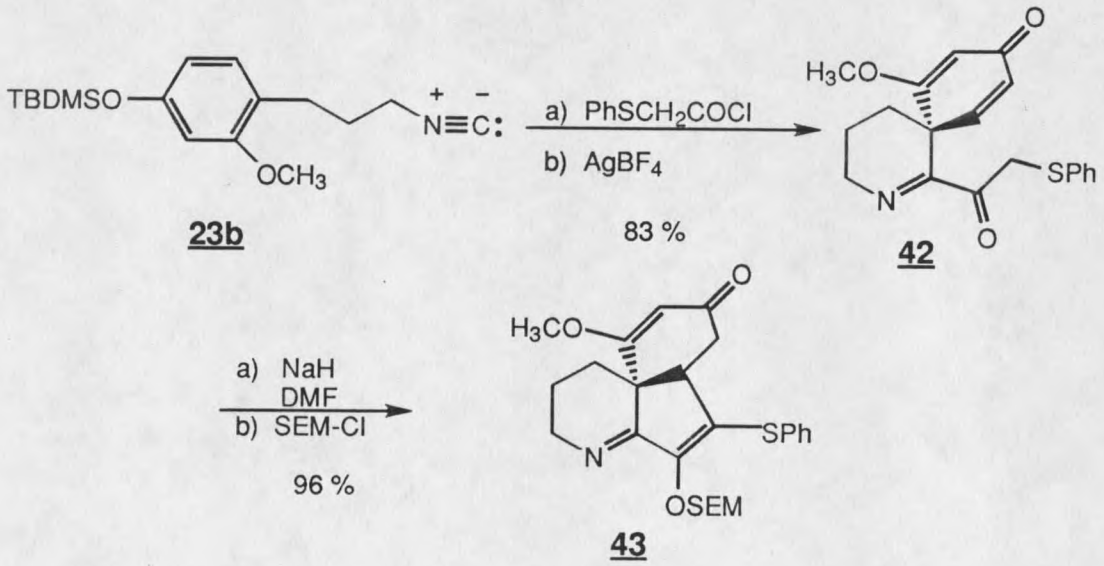
It was thought that an ideal candidate for this first attempt at forming the tricycle would be spirocycle **40**. However it was found that the yields in forming

this spirocycle were unusually low (55 %) and spirocycle **42**, obtained in 83 % yield, was used in its stead (Eq. 25 and Eq. 26). Thus treatment of **42** with NaH in DMF at 0 °C and warming to 25 °C resulted in the desired tricycle upon quenching with AcOH. However, this compound readily decomposed. It was found, much to our pleasure, that quenching the intermediate with SEM-Cl at -78 °C resulted in the stable tricycle **43** in 96 % yield. In this step the enolate that was created after the cyclization was trapped, thus eliminating one more acidic position within the resulting tricycle.



23b **40**

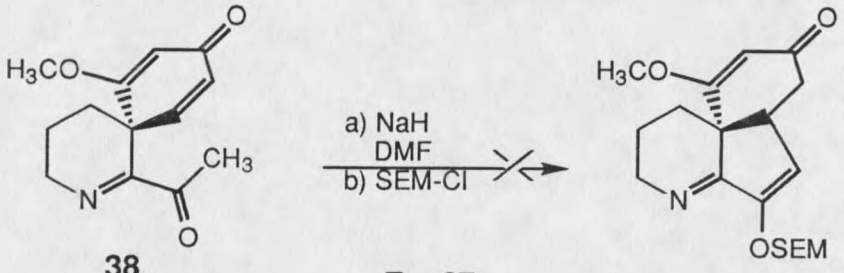
Eq. 25



23b **42** **43**

Eq. 26

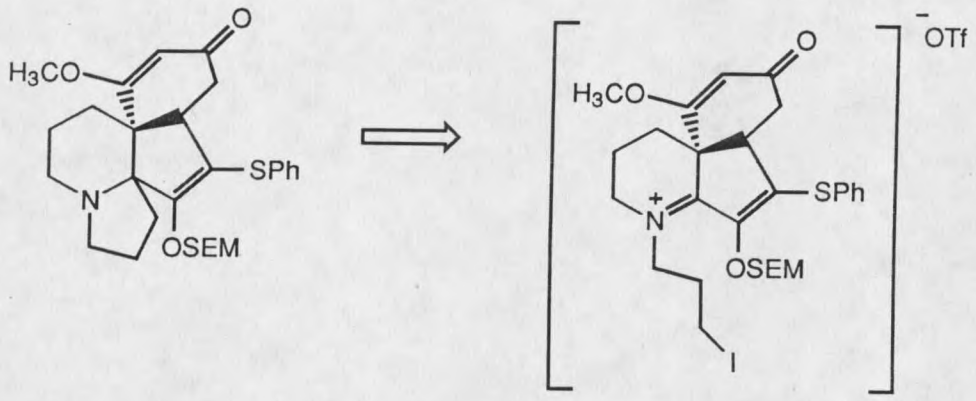
An attempt was made to form this third ring from the spirocycle **38** containing an acetyl moiety, however, no cyclized product was observed (Eq. 27).



38

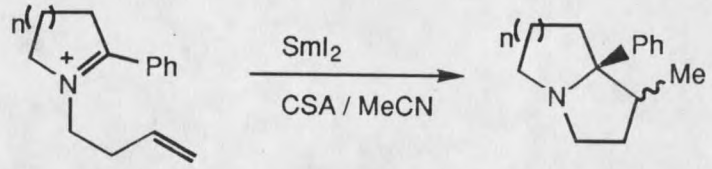
Eq. 27

With tricycle **43** in hand, several of the same intermolecular nucleophilic additions were attempted which had been tried previously with the spirocycle **27**. Once again, none of these attempts were successful. However, due to the additional functionality within the molecule, we were ready to pursue several new plans for the formation of the conclusive ring. The first method tried was based on the use of SmI_2 as a coupling agent.[47] It was believed that if the imine of the tricycle could be alkylated with 1-iodo-propanetrifluoromethanesulfonate and then treated with 2 equivalents of SmI_2, a single electron transfer (SET) from the SmI_2 would occur, resulting in reductive coupling of the iodide and the iminium salt (Scheme 22).



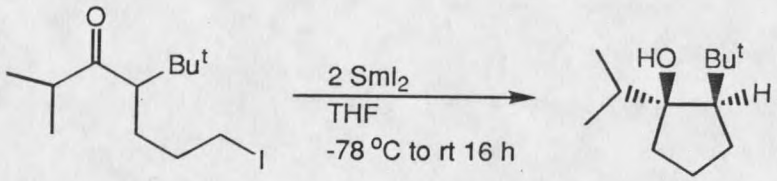
Scheme 22

No previous coupling of an iminium salt and a halogen by SmI_2 has previously been reported in the literature. A similar reaction has been reported by Martin[48] in which an α-amino radical formed by SET from SmI_2 couples with an olefin (Eq. 28).



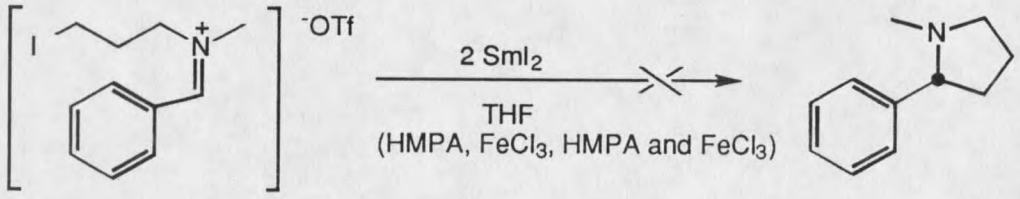
Eq. 28

However, there have been extensive studies on the coupling of sterically hindered aldehydes and ketones with halogens, an example of which, performed by Molander,[49] is shown in Eq. 29.



Eq. 29

Based on this information, several trial experiments were performed utilizing *N*-benzylidenemethylimine as a model to ascertain if this type of coupling was feasible. In proceeding with this plan, the imine was alkylated with the1-iodo-propanetrifluoromethanesulfonate and treated with SmI_2 under various conditions including the use of HMPA as a co-solvent, $FeCl_3$ as a SET catalyst,[50] and a combination of these additives, however, none of these conditions were successful (Eq 30).

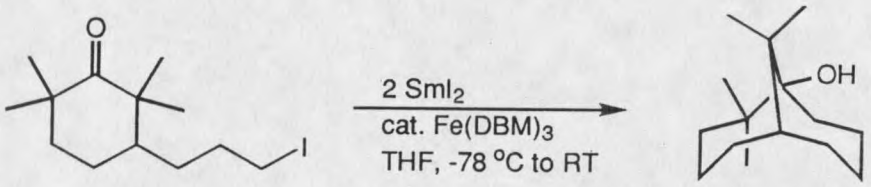


44

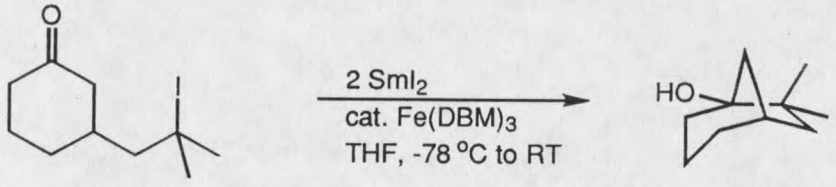
Eq. 30

Even more recent work by Molander has shown the use of $Fe(DBM)_3$ to be an excellent catalyst in the coupling of hindered ketones with iodides and also the coupling of hindered iodides with ketones[51] (Eq. 31 and Eq. 32). The application of these conditions to the model reaction was successful, resulting in the cyclic tertiary amine **45** in 52 % unoptimized yield (Eq. 33). Much to our

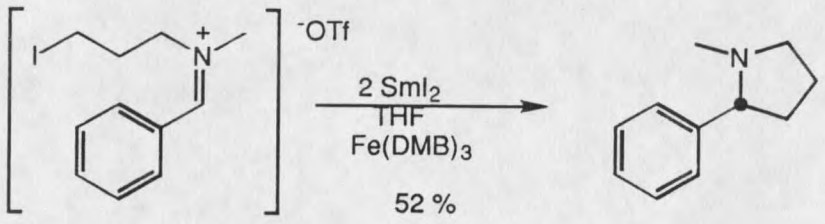
dismay, these conditions were not found to be compatible with the substrate of interest in the synthesis of the natural product (Eq. 34).



Eq. 31

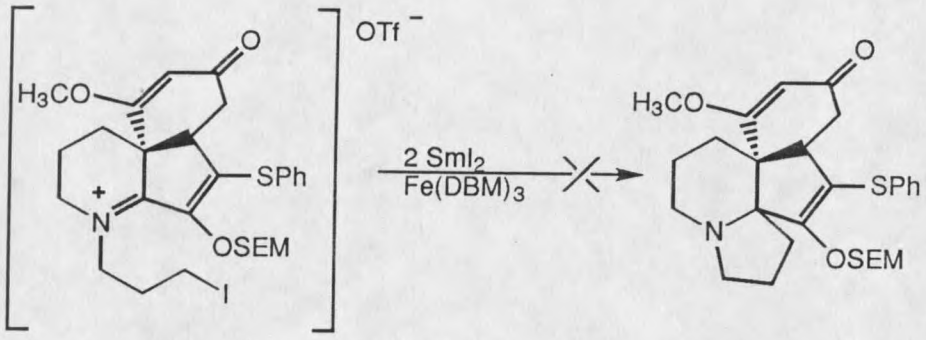


Eq. 32



44 **45**

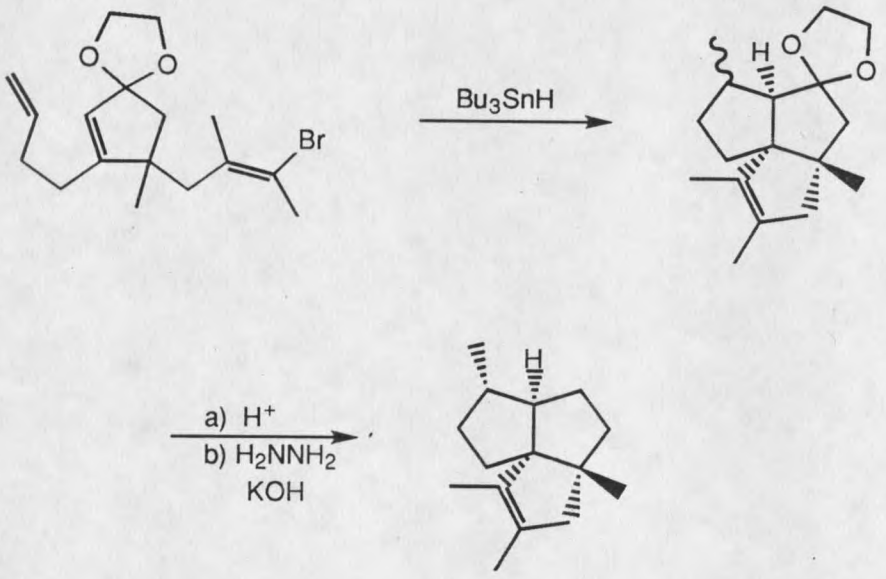
Eq. 33



46

Eq. 34

A further effort to functionalize the α,β-unsaturated imine and employ free radical methodology to close the final ring was undertaken. It has long been known that ring closure in extremely hindered environments can be achieved utilizing radicals, as seen by Curran's synthesis of silphiperfol-6-ene[52] (Eq. 35).

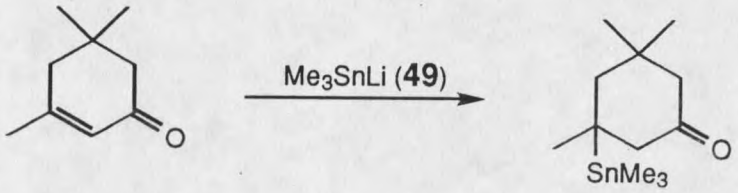


Silphiperfol-6-ene

Eq. 35

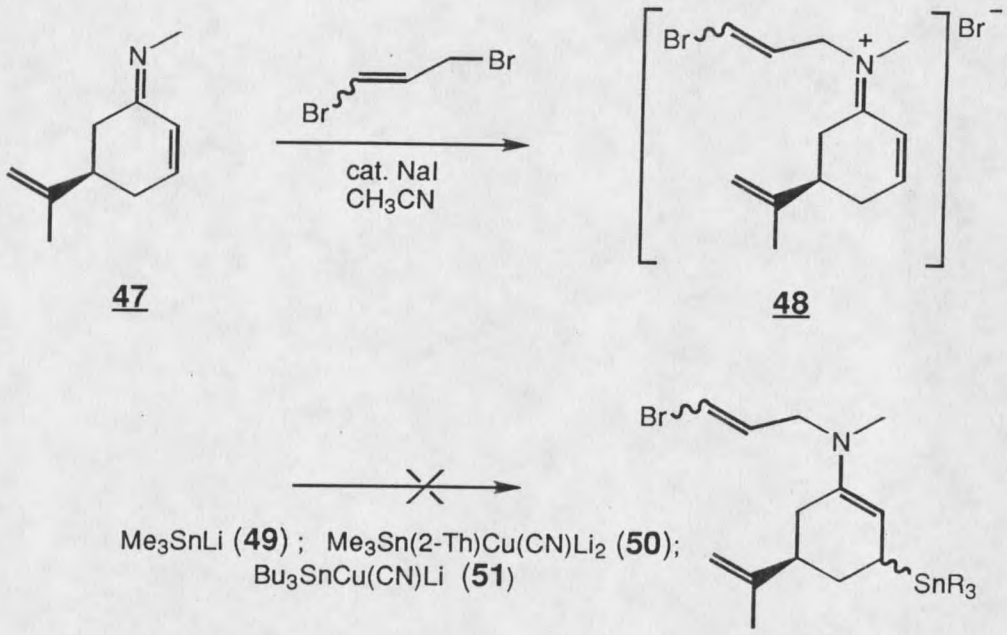
Knowing full well how hindered the imine carbon of tricycle **43** was, as demonstrated by the various attempts at further functionalization, it was hoped that this method would be successful in the closure of the elusive C ring. It was believed that upon forming the necessary iminium salt, a nucleophile could be introduced to the molecule via 1,4-addition. Subsequent 5-*exo*-trig radical ring closure would then result in the formation of the final ring of the serratine skeleton.

In order to perform the cyclization and allow the desired fragmentation to take place, a nucleophile must be introduced which will depart the molecule homolytically. An obvious choice would be to introduce a trialkyltin moiety. With this in mind, the work of Still[53] was examined in which it was found that nearly exclusive 1,4-additon is observed when lithium trimethyl- and tributyltin species are added to enones (Eq. 36).



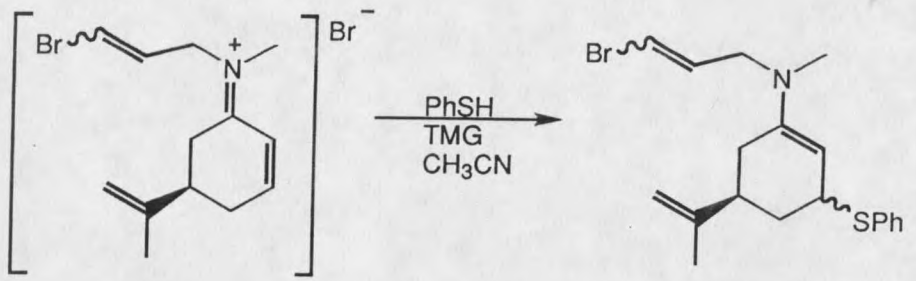
Eq. 36

Addition of this tin species **49**, as well as the higher order stannyl cuprate **50** and the lower order cuprate **51** derived from hexabutylditin, to the α,β-unsaturated iminium salt **48** was attempted, however, in each case decomposition of the starting material was observed (Eq. 37).



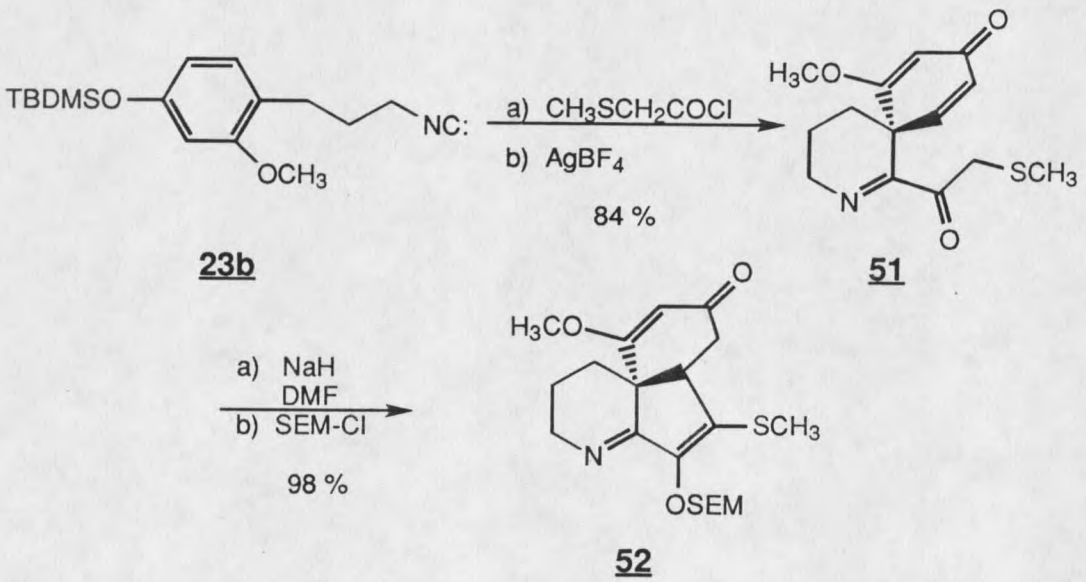
Eq. 37

In the belief that a milder nucleophile was needed to obtain clean introduction of a moiety suitable for the ensuing radical cyclization at the desired position of the molecule, nucleophilic additions of sulfur anions were then attempted. It was discovered that treating the iminium salt **48** with thiophenol and tetramethylguanidine resulted in clean 1,4-addition in a model study monitored by NMR (Eq. 38). Tricycle **52** was prepared to preclude the



48 Eq. 38 **49**

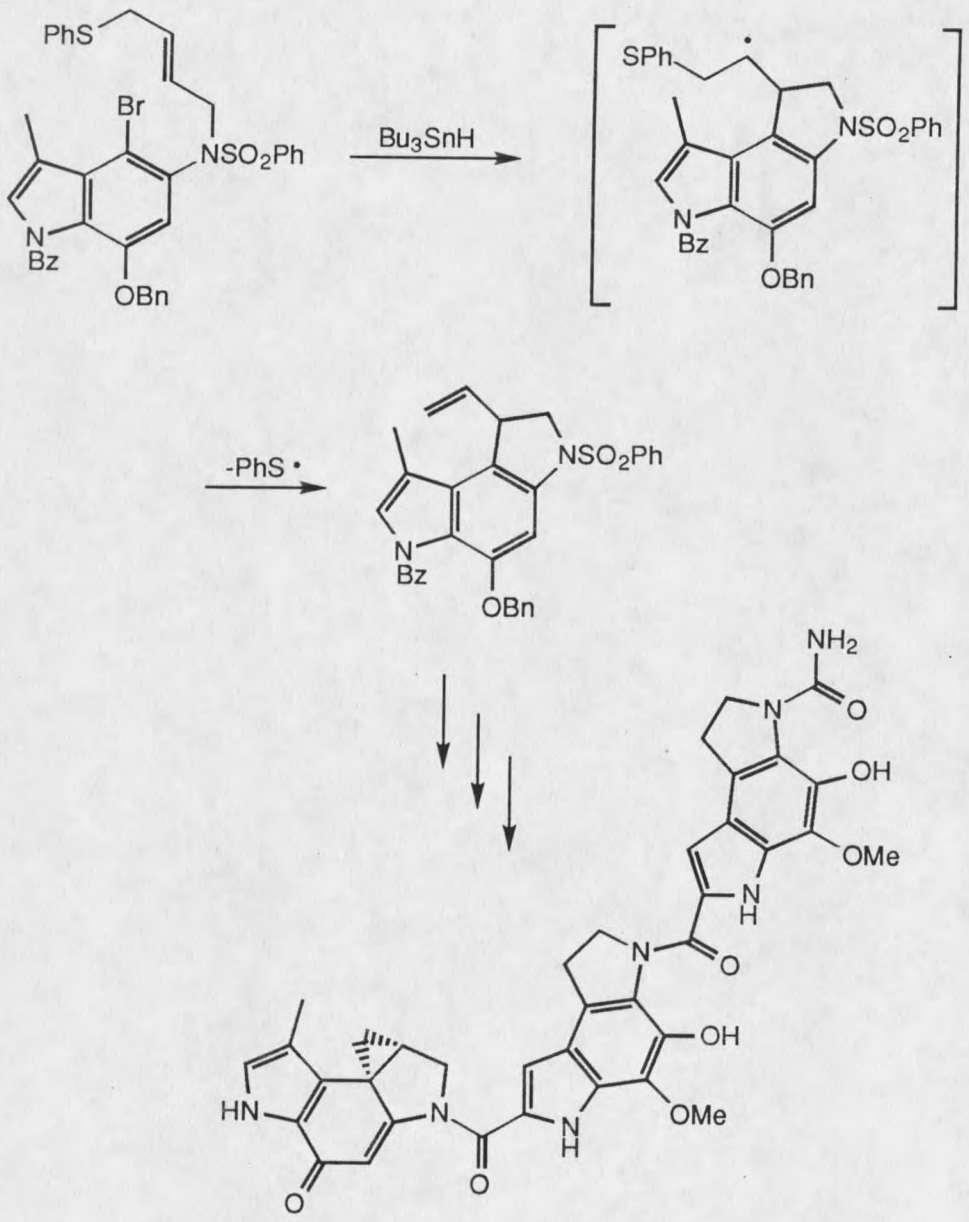
possibility of the thiophenol moiety as a site of steric hindrence for the 1,4-delivery of the sulfur anion to the conjugated iminium ion (Eq. 39). We then



23b **51** **52**

Eq. 39

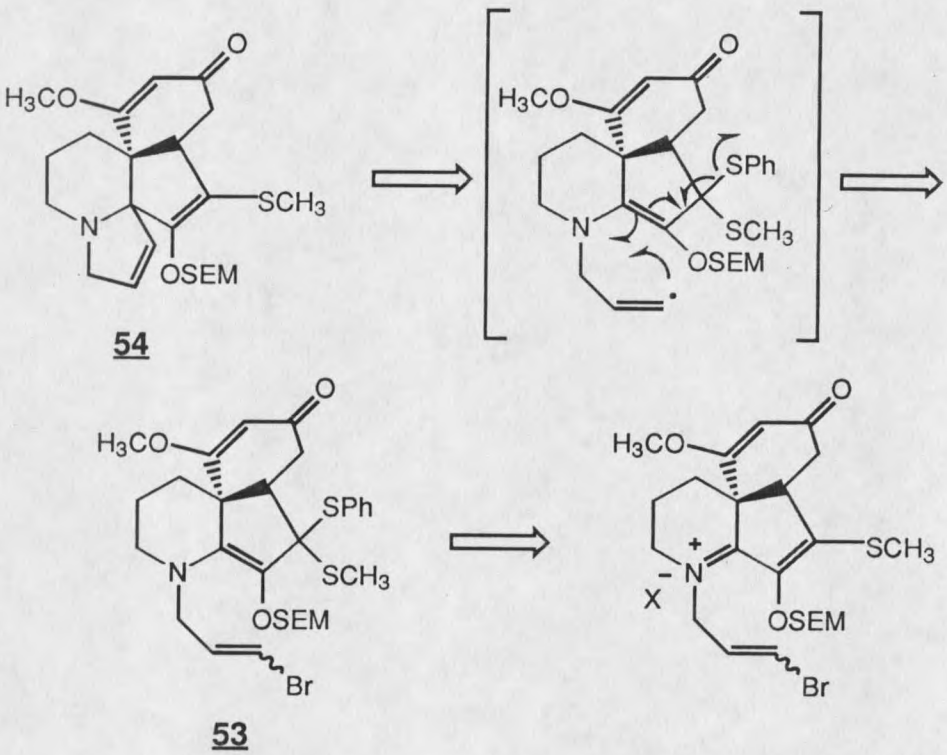
hoped that we could pursue a radical cyclization similar to one performed by Boger[54] in the synthesis of the antitumor-antibiotic (+)-CC-1065 (Scheme 23).



(+)-CC-1065

Scheme 23

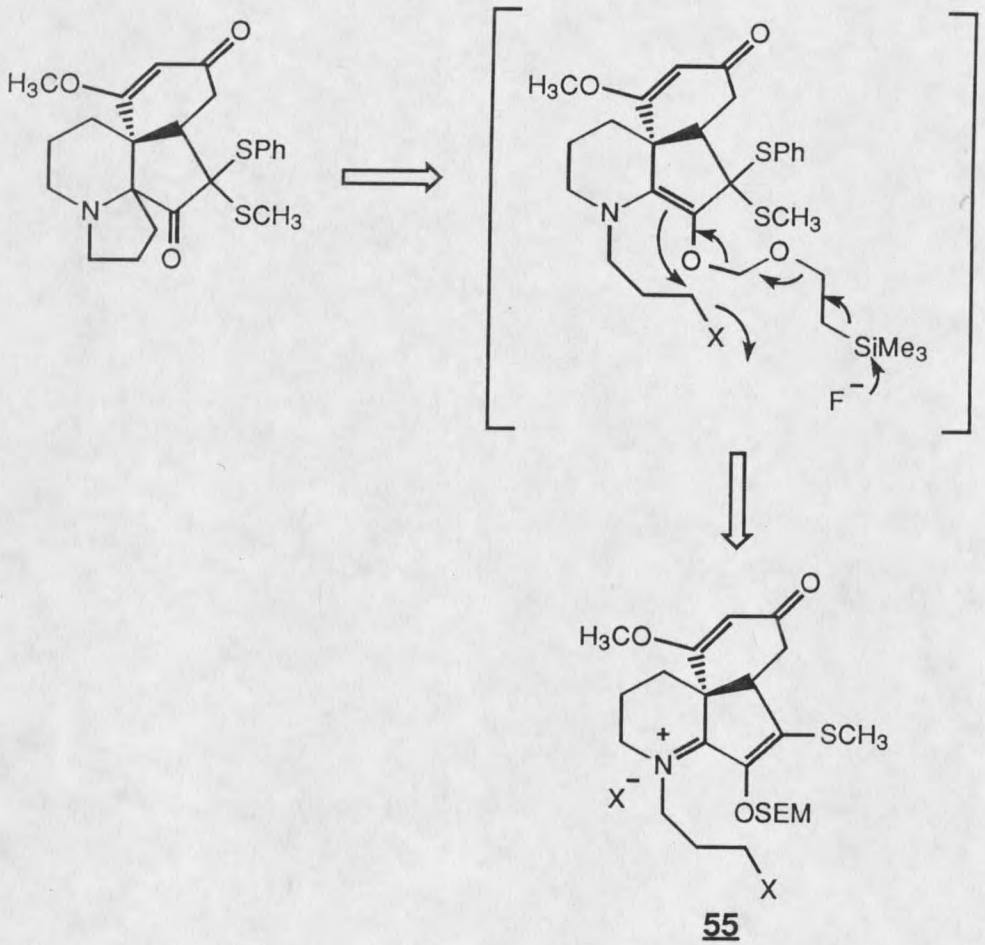
Conjugate addition of the sulfur anion to the iminium ion derived from tricycle **52** would afford the mixed thioacetal **53**, which upon formation of an initial vinyl radical,[55] could cyclize to form the tetracycle **54** (Scheme 24). Also upon addition to the conjugated iminium ion **55** the possibility existed to close the



54 **53**

Scheme 24

final ring by merely treating the resulting tricycle with a source of fluoride[56] (Scheme 25). However, once again our plans were thwarted when the precycle required for the natural product could not be isolated due to thermal instability.

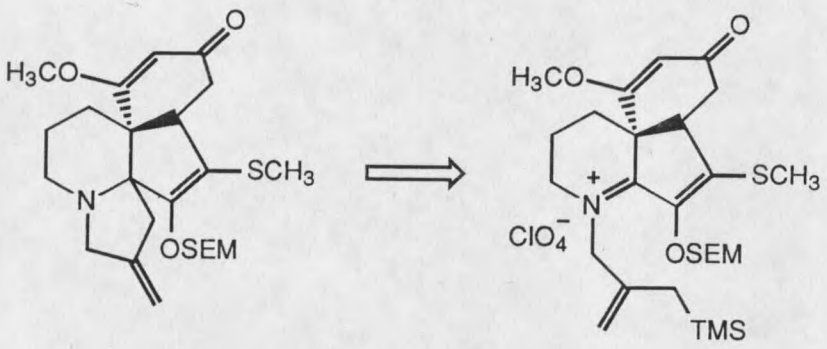


55

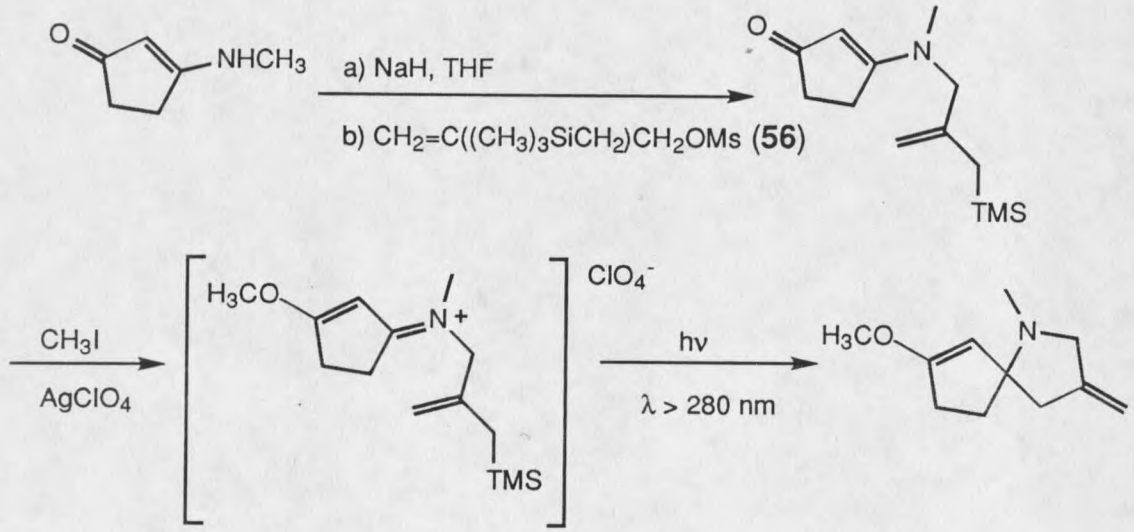
Scheme 25

One last effort to form the final ring was pursued. Work by Mariano[57] has shown that conjugated iminium salts can be induced to undergo photocyclizations with allylsilanes (Eq. 40). Of all previous attempts to form the remaining 5-membered ring, this work appeared the most analogous to our substrate. From a conjugated iminium ion, a quaternary site is formed which connects two five membered rings. However, the tetracycle derived from the cyclization of tricycle **52** would result in a ring containing an undesired exocyclic methylene moiety (Scheme 26). Even with this disadvantage, attempts were

made to functionalize an imine with the allyl mesylate **56** and the corresponding allyl iodide (**57**)[58] to yield the iminium salt directly.



Scheme 26



Eq. 40

Trost and Curran[59] have postulated that with these particular compounds, the steric bulk of the trimethylsilyl moiety blocks both the S_N2 and S_N2' sites of attack in the molecule as well as the leaving group (Figure 4). This problem was found to be significant in this case as well, for very little reaction

was seen with benzylidene methylimine (**58**) as a model substrate, even after 48 h at 70 °C in CD_3CN, a temperature which has been shown to cause the desired substrate (**52**) to decompose (Eq. 41).

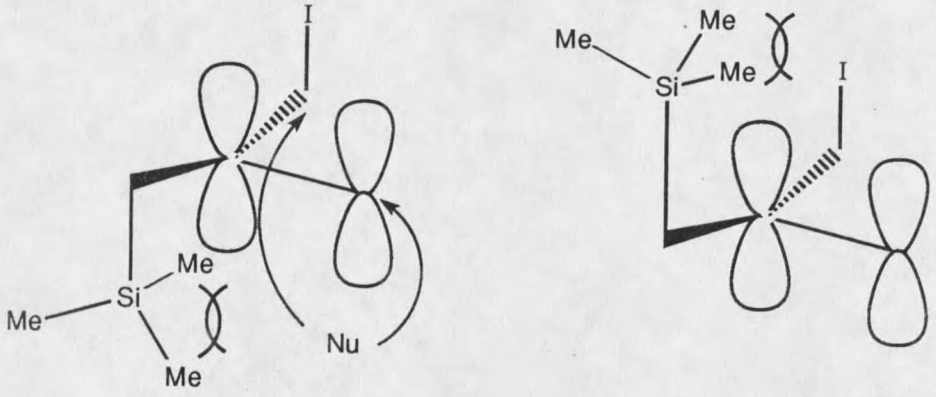
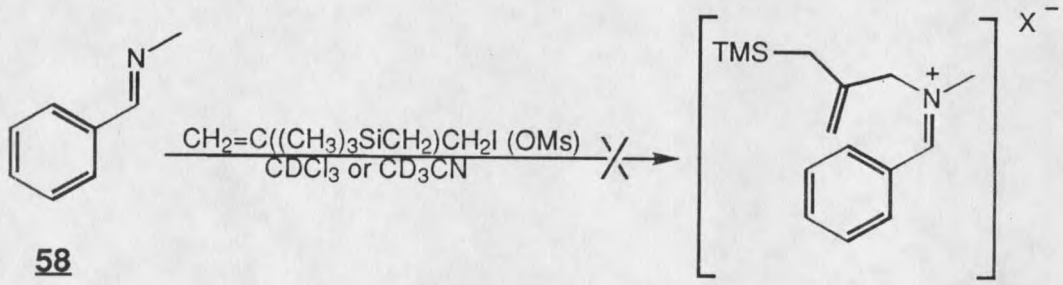


Figure 4. Blocking Effect of the Trimethylsilyl Moiety to Nucleophilic Addition and to Leaving Group in **57**.

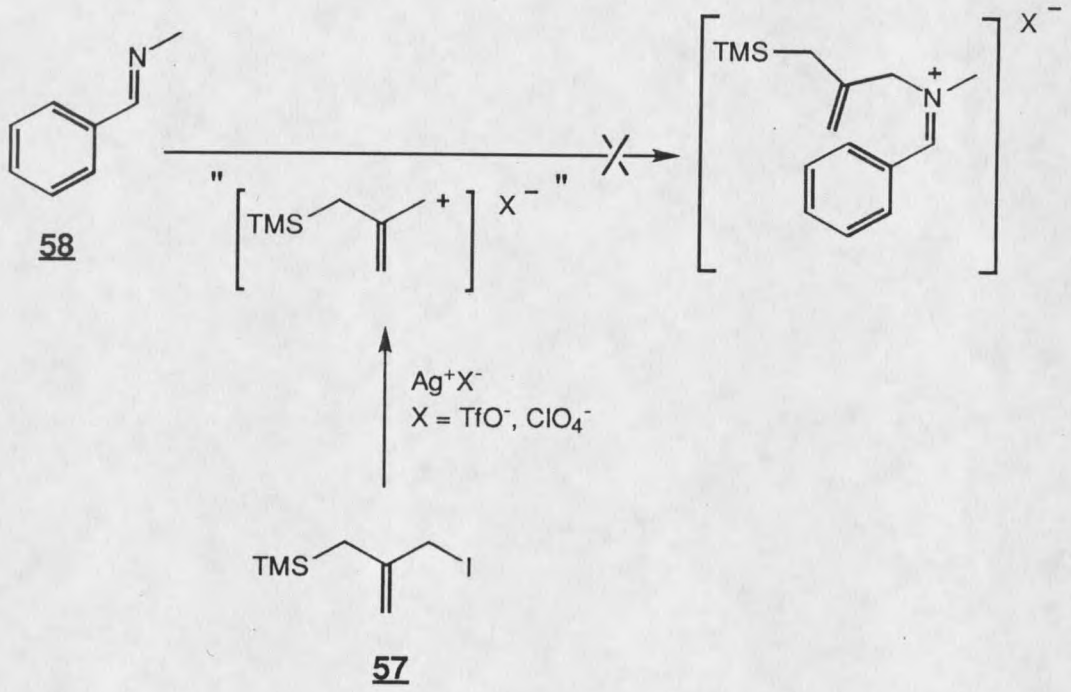


58

Eq. 41

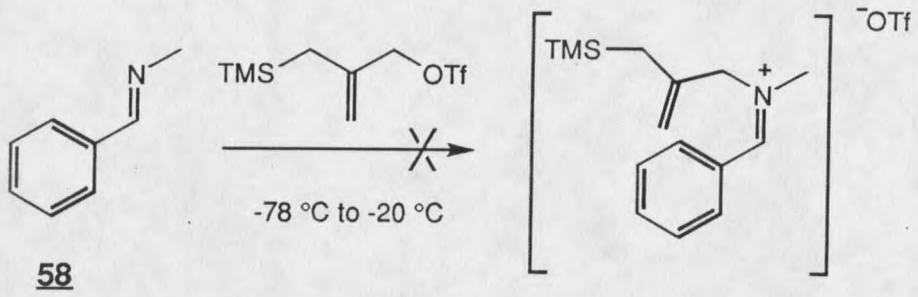
To increase the electrophilicity of the molecule, an attempt was made to generate the allyltriflate species from the allyl alcohol. However, this apparently extremely reactive species could not be isolated. Generation of the allyltriflate and allyl perchlorate species in situ from the allyl iodide was then investigated.

Both of these attempts resulted in decomposition of the allyl iodide with no addition to the imine (Scheme 27).



Scheme 27

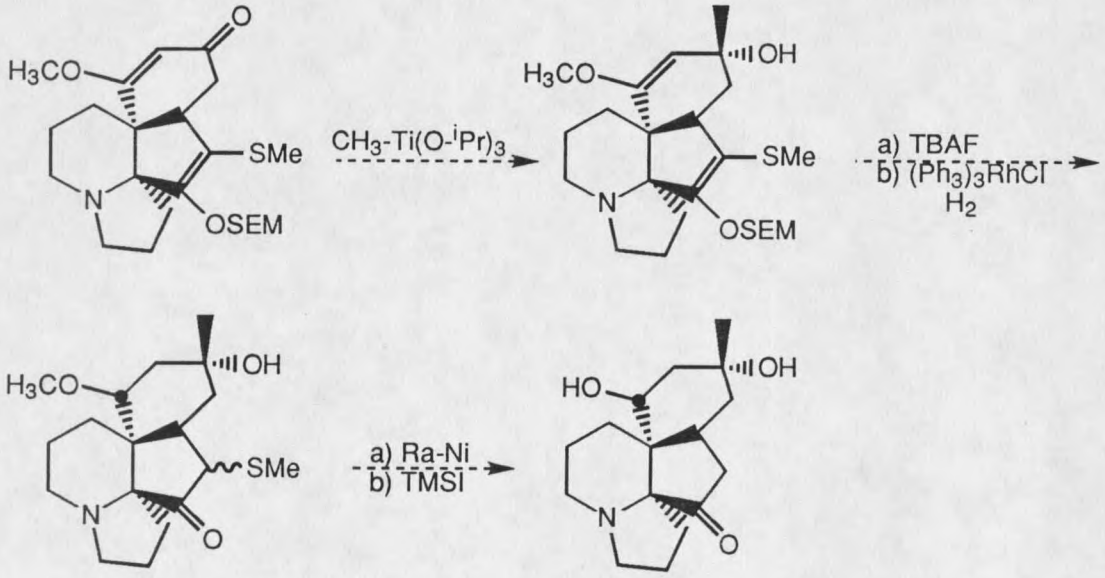
It was then hoped that the allyl triflate, when formed at -78 °C using conventional methods (Tf_2O, py, CH_2Cl_2), could be treated directly with the imine at that temperature to give the desired product. Even after separation of the triflate from the pyridine trifluoromethylsulfonate formed as the by-product in the reaction, no clean reaction was observed (Eq. 42).



58

Eq. 42

The closure of the D ring of serratine, with its sterically crowded environment, has remained elusive. However, if a method can be found to secure this last ring, there should be only a small number steps required to complete the synthesis of this natural product (Scheme 28).



Scheme 28

CONCLUSION

The use of acylnitrilium ion initiated cyclizations in the synthesis of azacycles has been expanded to include phenolic silyl ethers as reaction terminators. This new method allows for the formation of either spirocyclic 6 \ 6 or fused 6 \ 7 ring systems depending upon the position of electron donating substituents contained on the aromatic ring. Advances toward the synthesis of the *Lycopodium* alkaloid serratine have been established utilizing this methodology.

Difficulties were encountered in attempts to functionalize the imine moiety contained within the spirocycle used as the backbone in the formation of the skeleton of serratine. This was presumably due to the extremely sterically hindered environment in which the imine was located within the molecule.

Formation of the B ring of the serratine skeleton was accomplished through the conjugate addition of the enolate arising from the acyl moiety onto the unsubstituted enone contained within the D ring of the system. The enolate resulting from this cyclization was trapped with SEM-Cl, yielding a conjugated imine. This new functionality was utilized in various attempts to functionalize the imine and secure the final ring. Included in these attempts to close this ring was the use of SmI_2 to couple an iminium ion and an *N*-alkyliodide. This method was not successful in the cyclization of the compound required for the synthesis of the natural product, however, it was successful in a model compound.

EXPERIMENTAL

Physical Data: ^{1}H NMR and ^{13}C NMR were measured at 300 and 75 MHz, respectively, with a Bruker AC-300 spectrometer. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to the residual protons of $CDCl_3$ (δ 7.24). ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (δ 77.0). ^{1}H coupling constants are reported in Hz and refer to real or apparent multiplicities which are indicated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentet), br (broad), m (multiplet), app d (apparent doublet), app t (apparent triplet), etc.

Infrared spectra were recorded with either a Perkin Elmer 1800 FTIR or Bruker IFS 25 IR. High resolution mass spectra were measured on a VG Analytical 7070E spectrometer by Dr. L.J. Sears. Melting points were determined with a Fisher-Johns or a Mel-Temp II melting point apparatus and are uncorrected.

Chromatography: Gas chromatography was performed on a Varian Model 3700 Gas Chromatograph equipped with a flame ionization detector, a Hewlett-Packard 3390A Reporting Integrator and a 15m x 0.52mm ID column with a DB5, SE-45, or equivalent bonded phase.

Analytical thin layer chromatography was performed on silica gel K42-G plates supplied by Alltech Associates. Visualization of plates was effected by one or more of the following techniques: a) ultraviolet illumination (254 nm); b) exposure to iodine vapor; c) $KMnO_4$ oxidation; or d) anisaldehyde derivatization.

Column chromatography was performed using E. Merck silica gel 60 or Fisher Scientific 100-200 mesh Florisil®. Solvent systems used for elution are reported in % volume/volume.

Materials: Acetonitrile, benzene, 1,2-dichloroethane, dichloromethane, diisopropylamine, diisopropylethylamine, *N,N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA), hexane, pentane, and triethylamine were distilled under argon, nitrogen, or vacuum from calcium hydride. Dimethoxyethane and tetrahydrofuran (THF) were distilled under nitrogen from potassium. Diethylether was distilled under nitrogen from sodium benzophenone ketyl. Methanol was distilled from $Mg(OCH_3)_2$ under argon. Chloroform and carbontetrachloride were distilled under argon from phosphorous pentoxide. Thionyl chloride was distilled under argon from triphenylphosphite.

General Procedures: The molarities of organolithium reagents and Grignard reagents were determined by titration of a standard solution of 2-butanol in xylene using 1,10-phenanthroline or dipyridyl as an indicator.

Unless otherwise indicated, all reactions were carried out in flame or oven dried vessels under nitrogen or argon. Reaction mixtures were magnetically stirred unless mentioned otherwise. Transfer of sensitive liquids and solutions was accomplished by syringe or cannula and introduced to vessels through rubber septum caps. Temperatures reported are bath temperatures unless indicated otherwise. Concentrations were performed under reduced pressure with a Büchi (RE111) rotary evaportor and "drying" of an organic solution was accomplished with anhydrous $MgSO_4$ or Na_2SO_4.

4-*t*-Butyldimethylsilyloxybenzaldehyde (18a). To a solution of 4-hydroxybenzaldehyde (1.221 g, 10 mmol) in DMF (25 mL) was added t-butyldimethylchlorosilane (1.658 g, 11 mmol, 1.1 equiv) and imidazole (1.701 g, 25 mmol, 2.5 equiv). The reaction mixture was stirred for 12 h at 25 °C at which time it was quenched with sat. aqueous $NaHCO_3$ (10 mL) and extracted with hexane (3 x 15 ml). The combined organics were washed with H_2O (15 mL), dried ($MgSO_4$), and concentrated. Bulb to bulb distillation afforded 2.200 g (93 %) of **18a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H, -C**H**O), 7.76 (d, J=8.6 Hz, 2H, Ph), 6.91 (d, J=8.6 Hz, 2H, Ph), 0.96 (s, 9H, 3 C**H**$_3$), 0.21 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6 (CH), 161.42 (C), 131.79 (CH), 130.48 (C), 120.41 (CH), 25.51 (CH_3), 18.19 (C), -4.42 (CH_3); MS (EI) 179, 151, 91, 75.

2-Methoxy-4-*t*-butyldimethylsilyloxybenzaldehyde (18b). The title compound was prepared in a manner similar to **18a** from 1.522 g (10 mmol) of 4-hydroxy-2-methoxybenzaldehyde. Bulb to bulb distillation afforded 2.664 g (85 %) of **18b** as a white solid: m.p. 54 - 57 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.26 (s, 1H, -C**H**O), 7.71 (d, J=8.4 Hz, 1H, Ph), 6.44 (dd, J=8.6, 1.9 Hz, 1H, Ph), 6.37 (d, J=2.1 Hz, 1H, Ph), 3.84 (s, 3H, -OC**H**$_3$), 0.96 (s, 9H, 3 C**H**$_3$), 0.22 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.24 (CH), 163.68 (C), 162.97 (C), 130.36 (CH), 119.56 (C), 112.56 (CH), 103.38 (CH), 100.70 (C), 55.55 (CH_3), 25.56 (CH_3), 18.23 (C), -4.33 (CH_3); MS (EI) 266, 209, 161, 89, 44.

3-Methoxy-4-*t*-butyldimethylsilyloxybenzaldehyde (18c). This compound was prepared in a similar manner to **18a** but employing 0.746 g (4.9

mmol) of vanillin. Bulb to bulb distillation afforded 1.305 g (91 %) of **18c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H, -CHO), 7.34 (m, 2H, Ph), 6.92 (d, J=8 Hz, 1H, Ph), 3.82 (s, 3H, -OCH_3), 0.96 (s, 9H, 3 CH_3), 0.15 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.72 (CH), 151.61 (C), 151.29 (C), 130.99 (C), 125.99 (CH), 120.67 (CH), 110.32 (CH), 55.38 (CH_3), 25.55 (CH_3), 18.44 (C), -4.61 (CH_3); MS (EI) 265, 251, 194, 165, 50.

4-*t*-Butyldimethylsilyloxycinnamonitrile (19a). A solution of cyanomethylphosphonate (1.860 g, 10.5 mmol, 1.05 equiv) in THF (7.5 ml) was added to a suspension of NaH (0.264 g, 11 mmol, 1.1 equiv) in THF (15 ml) at 0 °C over 30 min. The mixture was then allowed to warm to 25 °C and was maintained at this temperature for 45 min. The reaction mixture was then cooled to 0 °C and a solution of aldehyde **18a** (2.364 g, 10 mmol) in THF (7.5 mL) was added dropwise over 20 min. The reaction mixture was then allowed to warm to 25 °C and was maintained at this temperature for 12 h. The mixture was then partitioned between H_20 (25 mL) and ethyl acetate (25 mL). The aqueous layer was separated and further extracted with ethyl acetate (2 x 25 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified by bulb to bulb distillation to yield 2.10 g (81 %) of **19a** as a clear oil. The product consisted of a mixture of *E* and *Z* isomers. Full characterization was provided following hydrogenation of the olefin in the subsequent step: MS (EI) 259, 244, 202, 186, 128, 101, 75, 43.

2-Methoxy-4-*t*-butyldimethylsilyloxycinnamonitrile (19b). This compound was prepared in a manner analogous to **19a** utilizing 2.263 g (8.5

mmol) of **18b**. Bulb to bulb distillation provided 2.23 g (91 %) of **19b**. The product consisted of a mixture of *E* and *Z* isomers. Full characterization was provided following hydrogenation of the olefin in the subsequent step: MS (EI) 289, 232, 202, 75, 73, 59.

3-Methoxy-4-*t*-butyldimethylsilyloxycinnamonitrile (19c). This cinnamonitrile was prepared in a manner analogous to **19a** from 2.539 g (9.5 mmol) of **18c**. Bulb to bulb distillation provided 2.71 g (98 %) of **19c**. The product consisted of a mixture of *E* and *Z* isomers. Full characterization was provided following hydrogenation of the olefin in the subsequent step: MS (EI) 289, 274, 232, 217, 202, 136, 59.

3,4-Methylenedioxycinnamonitrile (19d). To a solution of KOH (3.30 g, 50 mmol) in CH_3CN (40 mL) at reflux was added piperinal (7.50 g, 50 mmol) in CH_3CN (10 mL) rapidly by syringe. The reaction mixture was stirred at reflux for 20 min, then it was poured onto cracked ice (100 g) and then partitioned between the water and CH_2Cl_2 (20 mL). The aqueous layer was separated and then extracted further with CH_2Cl_2 (2 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated. Bulb to bulb distillation provided 8.60 g (99 %) of **19d** as a yellow solid. The product consisted of a mixture of *E* and *Z* isomers. Full characterization was provided following hydrogenation of the olefin in the subsequent step: MS (EI) 173, 114, 88, 62.

2-(4-*t*-Butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (20a). A hydrogenation apparatus was charged with olefin **19a** (5.182 g, 20.0 mmol) in

95 % EtOH (140 mL) and 10 % palladium on carbon (1.000 g). The mixture was placed under a 40 psi H_2 atmosphere and stirred at 25 °C for 18 h. The reaction mixture was then filtered through Celite. The organics were concentrated and purified by bulb to bulb distillation to provide 5.06 g (97 %) of **20a** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J=8.6 Hz, 2H, Ph), 6.78 (d, J=8.6 Hz, 2H, Ph), 2.86 (app t, J=7.3 Hz, 2H, C**H**$_2$), 2.57-2.52 (m, 2H, C**H**$_2$), 0.97 (s, 9H, 3 C**H**$_3$), 0.18 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.68 (C), 130.71 (C), 129.15 (CH), 120.24 (CH), 119.12 (C), 30.73 (CH_2), 25.56 (CH_3), 19.42 (CH_2), 18.07 (C), -4.54 (CH_3); MS (EI) 261, 204, 165, 130, 98, 75.

2-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (20b). This nitrile was prepared in a manner analogous to **20a** but employing 1.591 g (5.5 mmol) of **19b**. Bulb to bulb distillation provided 1.39 g (87 %) of **20b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J=8.0 Hz, 1H, Ph), 6.67 (m, 2H, Ph), 3.78 (s, 3H, OC**H**$_3$), 2.86 (app t, J=7.4 Hz, 2H, C**H**$_2$), 2.56 (app t, J=7.3 Hz, 2H, C**H**$_2$), 0.97 (s, 9H, 3 C**H**$_3$), 0.13 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.08 (C), 144.29 (C), 131.53 (C), 121.06 (CH), 120.41 (CH), 119.17 (C), 112.45 (CH), 55.53 (CH_3), 31.32 (CH_2), 25.68 (CH_3), 19.49 (CH_2), 18.38 (C), -4.66 (CH_3); MS (EI) 291, 234, 195, 130, 75.

2-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-eth-1-ylnitrile (20c). The title compound was prepared in a manner analogous to **20a** from 2.50 g (8.6 mmol) of **19c**. Bulb to bulb distillation provided 2.39 g (95 %) of **20c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J=8 Hz, 1H, Ph), 6.70-6.57 (m, 2H, Ph), 3.78 (s, 3H, OC**H**$_3$), 2.85 (app t, J=7.4 Hz, 2H, C**H**$_2$), 2.56 (app t, J=7.3 Hz, 2H, C**H**$_2$),

0.98 (s, 9H, 3 CH_3), 0.13 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.97 (C), 144.17 (C), 131.48 (C), 120.97 (CH), 120.33 (CH), 119.14 (C), 112.33 (CH), 55.79 (CH_3), 31.23 (CH_2), 25.63 (CH_3), 19.59 (CH_2), 18.32 (C), -4.73 (CH_3); MS (EI) 291, 261, 234, 219, 179, 121, 73, 59.

2-(3,4-Methylenedioxyphenyl)-eth-1-ylnitrile (20d). This compound was prepared in a manner analogous to **20a** utilizing 2.923 g (16.9 mmol) of **19d**. Bulb to bulb distillation provided 2.765 g (93 %) of **20d** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (m, 3H, Ph), 5.88 (s, 2H, OCH_2O), 2.80 (app t, J=7.2 Hz, 2H, CH_2), 2.52 (app t, J=7.2 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.64 (C), 146.42 (C), 131.61 (C), 121.10 (CH), 118.90 (C), 108.36 (CH), 100.80 (CH_2), 30.94 (CH_2); MS (EI) 175, 135, 77, 51.

3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylamine (21a). A solution of nitrile **20a** (0.523 g, 2.0 mmol) in Et_2O (2.7 mL) was added dropwise to a suspension of $LiAlH_4$ (0.080 g, 2.1 mmol, 1.05 equiv) over 30 min. The reaction mixture was maintained at 25 °C for 3 h at which time the mixture was cooled to 0 °C and quenched with the dropwise addition of H_2O (2.0 mL) followed by the addition of 15 % aqueous NaOH (2.0 mL) and then additional H_2O (6.0 mL). The resulting gray slurry was filtered through a fritted glass funnel. The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (2 x 10 mL). The combined wet organics were concentrated and the resulting oil was redissolved in a 1:1 mixture of CH_2Cl_2 and pentane, dried (Na_2SO_4), and concentrated once again, providing 0.501 g (94 %) of **21a** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (app d, J=8.3 Hz, 2H, Ph), 6.73 (app d, J=8.3

Hz, 2H, Ph), 2.68 (app t, J=7.0 Hz, 2H, CH_2), 2.56 (app t, J=7.7 Hz, 2H, CH_2), 1.71 (app p, J=7.4 Hz, 2H, CH_2-CH_2-CH_2), 1.35 (br s, 2H, -NH_2), 0.96 (s, 9H, 3 CH_3), 0.16 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.57 (C), 134.70 (C), 129.09 (CH), 119.78 (CH), 41.71 (CH_2), 35.53 (CH_2), 32.37 (CH_2), 25.65 (CH_3), 18.12 (C), -4.48 (CH_3).

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylamine (21b). This amine was prepared in a manner analogous to **21a** but employing 4.25 g (14.6 mmol) of **20b**, to provide 4.27 g (99%) of **21b** as a yellow oil.

This compound was also prepared from the azide **35** as follows: A flask was charged with 0.964 g (3.0 mmol) of **35**, 5 % palladium on carbon (150 mg), and EtOH (21 mL). This mixture was then placed under 1 atm of H_2 and stirred at 25 °C for 16 h. The mixture was then filtered through Celite and concentrated to yield 0.89 g (99 %) of **21b** a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.91-6.88 (m, 1H, Ph), 6.35-6.32 (m, 2H, Ph), 4.05 (br s, 2H, -NH_2), 3.75 (s, 3H, OCH_3), 2.67 (t, J=6.9 Hz, 2H, CH_2), 2.54 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 0.96 (s, 9H, 3 CH_3), 0.17 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.03 (C), 154.86 (C), 129.77 (CH), 122.79 (C), 111.31 (CH), 103.31 (CH), 55.14 (CH_3), 41.23 (CH_2), 33.52 (CH_2), 26.48 (CH_2), 25.65 (CH_3), 18.12 (C), -4.45 (CH_3); IR (film) 2930, 2857, 1608, 1584, 1504, 1466, 1413, 1389, 1362, 1291, 1255, 1201, 1161, 1120, 1038, 980, 840, 780 cm^{-1}.

3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylamine (21c). This compound was prepared in a similar manner to **21a** but employing 1.18 g (4.0 mmol) of **20c**, to afford 1.02 g (86 %) of **21c** as a yellow oil: ^1H NMR (300

MHz, $CDCl_3$) δ 6.78-6.57 (m, 3H, Ph), 3.75 (s, 3H, OCH_3), 2.67 (t, J=7.0 Hz, 2H, CH_2), 2.55 (t, J=7.7 Hz, 2H, CH_2), 1.71 (m, 2H, CH_2-CH_2-CH_2), 0.96 (s, 9H, 3 CH_3), 0.11 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.63 (C), 142.90 (C), 135.53 (C), 120.55 (CH), 120.35 (CH), 112.48 (CH), 55.41 (CH_3), 41.62 (CH_2), 35.43 (CH_2), 32.87 (CH_2), 25.67 (CH_3), 18.34 (C), -4.71 (CH_3).

3-(3,4-Methylenedioxyphenyl)-prop-1-ylamine (21d). The title compound was prepared in a similar manner to **21a** but employing 0.350 g (2.0 mmol) of **20d**, to afford 0.344 g (96 %) of **21d** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.68-6.56 (m, 3H, Ph), 5.84 (s, 2H, O-CH_2-O), 2.65 (m, 2H, CH_2), 2.52 (m, 2H, CH_2), 1.66 (m, 2H, CH_2-CH_2-CH_2), 1.20 (br s, 2H, -NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.40 (C), 145.39 (C), 135.84 (C), 120.85 (CH), 108.64 (CH), 107.92 (CH), 100.85 (CH_2), 41.51 (CH_2), 35.49 (CH_2), 32.24 (CH_2).

***N*-[3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (22a).** To amine **21a** (0.398 g, 1.5 mmol) was added ethyl formate (0.61 mL, 7.5 mmol). The resulting mixture was stirred at 25 °C for 16 h at which time it was concentrated. Chromatography (Florisil, ethyl acetate) yielded 0.426 g (97 %) of **22a** as a viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H, -NHC**H**O), 7.00 (d, J=8.3 Hz, 2H, Ph), 6.74 (d, J=8.5 Hz, 2H, Ph), 5.95 (br s, 1H, -**NH**CHO), 3.29 (app q, J=6.7 Hz, 2H, CH_2), 2.59-2.54 (m, 2H, CH_2), 1.84-1.75 (m, 2H, CH_2-CH_2-CH_2), 0.95 (s, 9H, 3 CH_3), 0.15 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.09 (CH), 153.85 (C), 133.78 (C), 129.13 (CH), 119.98 (CH), 37.77 (CH_2), 32.35 (CH_2), 31.20 (CH_2), 25.65 (CH_3), 18.14 (C), -4.47 (CH_3).

***N*-[3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (22b).** The title compound was prepared in a manner analogous to **22a** from 1.000 g (3.4 mmol) of **21b**. Chromatography (Florisil, ethyl acetate) yielded 1.064 g (97 %) of **22b** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H, -NHC**H**O), 6.90 (d, J=8.7 Hz, 1H, Ph), 6.34 (m, 2H, Ph), 5.97 (br s, 1H, -N**H**CHO), 3.74 (s, 3H, OC**H**$_3$), 3.24 (app q, J=6.6 Hz, 2H, C**H**$_2$), 2.57-2.52 (m, 2H, C**H**$_2$), 1.78-1.68 (m, 2H, CH_2-C**H**$_2$-CH_2), 0.96 (s, 9H, 3 C**H**$_3$), 0.19 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.10 (CH), 157.99 (C), 155.06 (C), 129.93 (CH), 122.22 (C), 111.47 (CH), 103.41 (CH), 55.20 (CH_3), 37.55 (CH_2), 29.71 (CH_2), 26.59 (CH_2), 25.63 (CH_3), 18.11 (C), -4.47 (CH_3); IR (film) 3286, 3060, 2954, 2931, 2858, 1665, 1609, 1584, 1505, 1470, 1413, 1385, 1362, 1291, 1255, 1203, 1161, 1120, 1038, 980, 939, 841, 781, 689 cm^{-1}.

***N*-[3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-yl]formamide (22c).** This formamide was prepared in a manner analogous to **22a** but employing 0.315 g (1.1 mmol) of **21c**. Chromatography (Florisil, ethyl acetate) yielded 0.337 g (95 %) of **22c** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H, -NHC**H**O), 6.78-6.57 (m, 3H, Ph), 5.68 (br s, 1H, -N**H**CHO), 3.76 (s, 3H, OC**H**$_3$), 3.29 (app q, J=6.7 Hz, 2H, C**H**$_2$), 2.58- 2.53 (m, 2H, C**H**$_2$), 1.85-1.75 (m, 2H, CH_2-C**H**$_2$-CH_2), 0.96 (s, 9H, 3 C**H**$_3$), 0.11 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.07 (CH), 150.81 (C), 143.24 (C), 134.64 (C), 120.75 (CH), 120.37 (CH), 112.48 (CH), 55.49 (CH_3), 37.80 (CH_2), 32.87 (CH_2), 31.18 (CH_2), 25.70 (CH_3), 18.39 (C), -4.67 (CH_3).

***N*-[3,4-Methylenedioxyphenyl)-prop-1-yl]formamide (22d).** This compound was prepared in a manner analogous to **22a** from 0.269 g (1.5 mmol) of **21d**. Chromatography (Florisil, ethyl acetate) yielded 0.293 g (94 %) of **22d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H, -NHC**H**O), 6.71-6.54 (m, 3H, Ph), 5.88 (s, 2H, O-C**H**$_2$-O,), 3.27 (app q, J=6.7 Hz, 2H, C**H**$_2$), 2.58-2.51 (m, 2H, C**H**$_2$), 1.82-1.73 (m, 2H, CH_2-C**H**$_2$-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.51, 147.64, 145.76, 134.93, 121.02, 108.68, 108.15, 100.74, 37.61, 32.82, 31.27.

3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (23a). To a solution of formamide **22a** (0.293 g, 1.0 mmol) and Et_3N (0.505 g, 5.0 mmol, 5 equiv) in THF (3 mL) at 0 °C was added a solution of $POCl_3$ (0.169 g, 1.1 mmol, 1.1 equiv) in THF (0.1 mL) dropwise over 15 min. The reaction mixture was stirred for an additional 1.5 h at 0 °C at which time it was quenched by adding ice water (5 mL). Stirring was continued at 0 °C for a further 2 h. The aqueous layer was then separated and extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Chromatography (silica gel, 20 % ethyl acetate/hexane) provided 254 mg (92 %) of **23a** as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J=8.3 Hz, 2H, Ph), 6.78 (d, J=8.5 Hz, 2H, Ph), 3.35-3.29 (m, 2H, C**H**$_2$), 2.70 (app t, J=7.3 Hz, 2H, C**H**$_2$), 1.98-1.89 (m, 2H, C**H**$_2$,), 0.98 (s, 9H, 3 C**H**$_3$), 0.20 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.27 (C), 154.03 (C), 132.27 (C), 129.20 (CH), 120.01 (CH), 40.45 (CH_2), 31.20 (CH_2), 30.58 (CH_2), 25.55 (CH_3), 18.04 (C), -4.56 (CH_3); IR (film) 3030, 2955, 2931, 2859, 2147, 1609, 1511, 1472, 1390, 1362, 1260, 1170, 1105, 1008, 916, 840, 781cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (23b). The title compound was prepared in a manner analogous to **23a** but employing 5.97 g (18.5 mmol) of **22b**. Chromatography (silica gel, 20 % ethyl acetate/hexane) provided 4.87 g (86 %) of **23b** as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J=8.7 Hz, 1H, Ph), 6.37-6.33 (m, 2H, Ph), 3.75 (s, 3H, OC**H**$_3$), 3.33-3.28 (m, 2H, C**H**$_2$), 2.66 (m, 2H, C**H**$_2$), 1.94-1.88 (m, 2H, C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.50 (C), 155.46 (C), 130.21 (CH), 121.00 (C), 111.35 (CH), 103.46 (CH), 55.14 (CH_3), 40.92 (CH_2), 29.33 (CH_2), 26.48 (CH_2), 25.68 (CH_3), 18.17 (C), -4.41 (CH_3); IR (film) 2956, 2931, 2858, 2146, 1609, 1584, 1505, 1453, 1414, 1362, 1292, 1258, 1203, 1161, 1118, 1038, 979, 939, 842, 781 cm^{-1}.

3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (23c). This compound was prepared in a manner analogous to **23a** but employing 0.323 g (1.0 mmol) of **22c**. Chromatography (silica gel, 20 % ethyl acetate/hexane) provided 296 mg (97 %) of **23c** as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J=6.8 Hz, 1H, Ph), 6.66-6.59 (m, 2H, Ph), 3.83 (s, 3H, OC**H**$_3$), 3.35-3.30 (m, 2H, C**H**$_2$), 2.70 (app t, J=7.4 Hz, 2H, C**H**$_2$), 2.00-1.89 (m, 2H, C**H**$_2$), 0.98 (s, 9H, 3 C**H**$_3$), 0.13 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.91 (C), 143.58 (C), 133.12 (C), 120.88 (CH), 120.51 (CH), 112.56 (CH), 55.48 (CH_3), 40.58 (CH_2), 31.80 (CH_2), 30.64 (CH_2), 25.69 (CH_3), 18.38 (C), -4.68 (CH_3).

3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (23d). This isonitrile was prepared in a manner analogous to **23a** using 2.070 g (10 mmol) of **22d**. Chromatography (silica gel, 20 % ethyl acetate/hexane) provided 1.820 g (96 %) of **23d** as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, J=7.8 Hz, 1H, Ph), 6.65-6.60 (m, 2H, Ph), 5.89 (s, 2H, O-C**H**$_2$-O), 3.35-3.30 (m, 2H, C**H**$_2$), 2.68 (app t, J=7.3 Hz; 2H, C**H**$_2$), 1.97-1.86 (m, 2H, C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.42 (C), 147.75 (C), 146.03 (C), 133.44 (C), 121.23 (CH), 108.24 (CH), 100.81 (CH_2), 40.44 (CH_2), 31.79 (CH_2), 30.64 (CH_2); IR (film) 2928, 2360, 2149, 1608, 1503, 1489, 1443, 1349, 1246, 1189, 1100, 1039, 928, 866, 810 cm^{-1}.

7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (25a). An oven-dried NMR tube fitted with a rubber septem was purged with Ar and then charged with **23a** (0.138 g, 0.50 mmol), trimethylacetyl chloride (0.068 mL, 0.55 mmol), and $CDCl_3$ (0.25 mL). The insertion reaction was monitored by NMR and found to be complete after 180 min. The volatile components were then removed from the imidoyl chloride in vacuo. The crude imidoyl chloride was diluted with CH_2Cl_2 (2.25 mL), 1,2-dichloroethane (2.25 mL) and cooled to -78 °C. The solution was then added dropwise via syringe to a stirred solution of $AgBF_4$ (1.50 mL, 0.50 M in 1,2-dichloroethane, 0.75 mmol, 1.5 equiv) and CH_2Cl_2 (1.50 mL) maintained at -78 °C. After the addition, the reaction mixture was stirred for 1 h at -78 °C and then maintained at -20 °C for 20 h whereupon it was quenched with 10 % aqueous $KHCO_3$ (15 mL). The resulting white-gray slurry was subsequently filtered through a pad of celite. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4 x 10 mL). The

combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and concentrated. Chromatography (silica gel, 20 % ethyl acetate/hexane) yielded 86 mg (70 %) of **25** as a yellow crystalline solid: m.p. 51-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J=8.4 Hz, 2H, **H**C=CH), 6.98 (d, J=8.4 Hz, 2H, HC=C**H**), 3.35 (m, 2H, C**H**$_2$), 2.77 (app t, J=7.4 Hz, 2H, C**H**$_2$), 1.96 (m, 2H, C**H**$_2$), 1.33 (s, 9H, 3 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 156.1, 149.6, 137.0, 129.2, 121.5, 40.6, 38.9, 31.4, 30.4, 30.0, 26.2; IR (KBr) 3032, 2980, 2930, 2874, 1744, 1680, 1509, 1481, 1454, 1368, 1281, 1228, 1198, 1167, 1126 cm^{-1}; MS (EI) 245, 161, 134, 107, 85, 57, 41; high resolution mass spectrum calcd. for $C_{15}H_{19}NO_2$: M^+ =245.1416. Found: M^+ =245.1410.

1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (25b). This spirocycle was prepared in a similar manner to **25a** but employing 0.073 g (0.24 mmol) of **23b**. Chromatography (silica gel, 5 % THF/CH_2Cl_2) yielded 54 mg (82 %) of **25b** as a yellow crystalline solid: m.p. 138-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J=9.9 Hz, 1H, Ph), 6.19 (d, J=9.8 Hz, 1H, Ph), 5.57 (s, 1H, Ph), 4.12-4.03 (m, 1H, C**H**H-N=C-C=O), 3.91-3.80 (m, 1H, CH**H**-N=C-C=O), 3.65 (s, 3H, OC**H**$_3$), 2.18-2.10 (m, 1H, **H**CH), 1.81-1.67 (m, 3H, HC**H**-C**H**$_2$), 1.19 (s, 9H, 3 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.10, 187.15, 177.30, 161.52, 145.56, 127.50, 102.38, 55.60, 49.02, 46.33, 43.67, 33.80, 27.43, 17.86; IR (KBr) 3062, 2956, 1684, 1662, 1638, 1594, 1456, 1438, 1368, 1234, 1214, 1090, 1016, 930, 880 cm^{-1}; MS (EI) 275, 191, 164, 137, 57, 41; high resolution mass spectrum calcd. for $C_{16}H_{21}NO_3$: M^+ =275.1521. Found: M^+ =275.1526.

1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (25c). This compound was prepared in a manner analogous to **25a** but employing 0.153 g (0.5 mmol) of **23c**. Chromatography (silica gel, 20 % ethyl acetate/hexane) furnished 195 mg (65 %) of **25c** as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H, Ph), 6.68 (s, 1H, Ph), 3.81 (s, 3H, OC**H**$_3$), 3.38 (app t, J=6.7 Hz, 2H, C**H**$_2$), 2.55 (app t, J=7.3 Hz, 2H, C**H**$_2$), 2.38-2.29 (m, 2H, C**H**$_2$), 1.25 (s, 9H, 3 C**H**$_3$), 0.11 (s, 6H, 2 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 209.39, 170.82, 152.19, 143.09, 134.53, 125.22, 120.18, 112.61, 55.42, 49.79, 43.74, 34.65, 30.65, 27.11, 25.71, 18.41, -4.64; IR (film) 2955, 2858, 1694, 1564, 1508, 1464, 1344, 1325, 1284, 1261, 1087, 907, 862, 840, 808, 784 cm^{-1}; MS (EI) 389, 332, 304, 276, 248, 233, 204, 73, 57, 41; high resolution mass spectrum calcd. for $C_{22}H_{35}NO_3Si$: M^+ =389.2386. Found: M^+ =389.2386.

1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (25d). The title compound was prepared in a manner analogous to **25a** but employing 0.095 g (0.5 mmol) of **23d**. Chromatography (20 % ethyl acetate/hexane) provided 97 mg (71 %) of **25d** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H, Ph), 6.68 (s, 1H, Ph), 5.94 (s, 2H, O-C**H**$_2$-O), 3.37 (app t, J=6.7 Hz, 2H, C**H**$_2$), 2.48 (app t, J=7.3 Hz, 2H, C**H**$_2$), 2.35-2.26 (2, C**H**$_2$), 1.25 (s, 9H, 3 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.95, 169.88, 148.74, 146.04, 135.26, 126.31, 109.31, 107.90, 101.33, 49.57, 43.89, 34.70, 30.57, 27.15; IR (film) 2954, 2864, 2362, 2362, 2338, 1686, 1654, 1596, 1558, 1540, 1506, 1484, 1362, 1240, 1040, 932, 882 cm^{-1}; MS (EI) 273, 188, 160, 131, 103, 57, 41; high resolution mass spectrum calcd. for $C_{16}H_{19}NO_3$: M^+ =273.1365.

Found: M^+ =273.1354.

1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (27). The title compound was prepared in a manner analogous to **25a** using 0.305 g (1.0 mmol) of **23b** and 0.162 g (1.1 mmol, 1.1 equiv) of dichloroacetyl chloride. Chromatography (silica gel, 50 % ethyl acetate/hexane) provided 0.240 g (80 %) of **28** as a yellow crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H, C**H**Cl_2), 6.53 (d, J=10.0 Hz, 1H, C**H**=CH), 6.20 (d, J=9.9 Hz, 1H, CH=C**H**), 5.59 (s, 1H, CH_3OC=C**H**), 4.26-4.12 (m, 1H, **H**CH-N=C), 3.94-3.83 (m, 1H, HC**H**-N=C), 3.61 (s, 3H, O**CH**$_3$), 2.18-2.08 (m, 1H, **H**CH), 1.88-1.72 (m, 3H, HC**H**-C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.71, 183.62, 176.00, 160.07, 143.14, 128.88, 102.39, 65.54, 55.83, 50.34, 45.60, 33.37, 17.80; IR (film) 2942, 1732, 1660, 1637, 1594, 1456, 1362, 1224, 1177, 1017, 941, 854, 806 cm^{-1}; MS (EI) 301, 191, 164, 136, 100, 91, 77, 65, 51; high resolution mass spectrum calcd. for $C_{13}H_{13}Cl_2NO_3$; M^+ =301.0272. Found: M^+ =301.0266.

3-(Prop-1-ene)-phenol (29). A solution of resorcinol (27.528 g, 250 mmol) in DMF (100 mL) was added to a suspension of NaH (6.312 g, 263 mmol, 1.05 equiv) in DMF (250 mL) at 0 °C over 30 min. The mixture was then allowed to warm to 25 °C and was maintained at that temperature for 1 h. The reaction mixture was then cooled to -10 °C and allyl bromide (22.744 g, 75 mmol, 0.75 equiv) in DMF (150 ml) was added over 30 min. The resultant mixture was allowed to warm to 25 °C and was maintained at that temperature for an additional 12 h whereupon it was quenched by adding H_2O (200 ml) to the solution at 0 °C. The mixture was extracted with CH_2Cl_2 (4 x 150 mL) and

the organics were washed with H_2O (4 x 100 mL) to remove any residual resorcinol. Residual diallylated product was removed by treating the organics with 5 % aqueous NaOH until basic. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and then acidified with 5 % aqueous HCl followed by extraction with CH_2Cl_2 (4 x 150 mL). The combined organics were dried (Na_2SO_4) and concentrated to yield 26.16 g (86 %) of **29** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, J=8.5 Hz, 1H, Ph), 6.51-6.47 (m, 1H, Ph), 6.43-6.39 (m, 2H, Ph), 6.09-5.96 (m, 1H, -OCH_2CH=CH_2), 5.42-5.25 (m, 1H, -CH=CH_2), 4.49 (m, 2H, -OCH_2CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.10 (C), 156.74 (C), 133.28 (CH), 130.11 (CH), 117.58 (CH_2), 108.01 (CH), 107.37 (CH), 102.50 (CH), 68.91 (CH_2); IR (film) 3347, 3082, 2931, 2873, 1663, 1596, 1491, 1463, 1387, 1284, 1266, 1176, 1148, 737 cm^{-1}.

3-(Prop-2-enoxy)-*t*-butyldimethylsilyloxyphenol (30). This compound was prepared in a manner analogous to **18a** but employing 3.130 g (20.8 mmol) of **29**. Bulb to bulb distillation afforded 5.056 g (92 %) of **30** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (t, J=8.1 Hz, 1H, Ph), 6.53-6.40 (m, 3H, Ph), 6.08-5.99 (m, 1H, OCH_2CH=CH_2), 5.42-5.23 (m, 2H, OCH_2CH=CH_2), 4.50-4.48 (m, 2H, OCH_2CH=CH2), 0.96 (s, 9H, 3 CH_3), 0.18 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.76 (C), 156.83 (C), 133.42 (CH), 129.63 (CH), 117.51 (CH_2), 112.80 (CH), 107.77 (CH), 107.20 (CH), 68.86 (CH_2), 25.70 (CH_3), 18.21 (C), -4.41 (CH_3); IR (film) 2930, 2859, 1596, 1489, 1259, 1177, 1148, 999, 926, 840, 781, 687 cm^{-1}.

3-[(4-*t*-Butyldimethylsilyloxy)phen-2-ol]-prop-1-ene (31). A solution of Et_2AlCl (35.0 mL, 1.0 M in hexane, 35.0 mmol, 1.1 equiv) was added to a solution of **30** (8.41 g, 31.8 mmol) in CH_2Cl_2 (64 mL) at -35 °C over 4 h. The reaction mixture was maintained at this temperature for an additional 12 h whereupon it was quenched by the careful dropwise addition of 5 % aq. HCl (100 mL) at 0 °C. The aqueous layer was separated and further extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated. Chromatography on silica gel (10 % ethyl acetate/hexane) yielded 6.58 g (78 %) of **31** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J=8.1 Hz, 1H, Ph), 6.39-6.34 (m, 2H, Ph), 6.06-5.92 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.17-5.13 (m, 1H, $CH_2CH=C\mathbf{H}H$), 5.11-5.10 (m, 1H, $CH_2CH=CH\mathbf{H}$), 5.01 (br s, 1H, O**H**), 3.33 (app d, J=6.3 Hz, 2H, $C\mathbf{H}_2CH=CH_2$), 0.96 (s, 9H, 3 $C\mathbf{H}_3$), 0.18 (s, 6H, 2 $C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.49 (C), 154.80 (C), 136.85 (CH), 130.65 (CH), 118.06 (C), 116.13 (CH_2), 112.62 (CH), 107.96 (CH), 34.56 (CH_2), 25.68 (CH_3), 18.18 (C), -4.44 (CH_3); IR (film) 3436, 2956, 2931, 2896, 2859, 1616, 1591, 1515, 1472, 1425, 1362, 1295, 1256, 1171, 1114, 988, 913, 869, 840, 781 cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ene (32). A solution of phenol **31** (6.580 g, 24.9 mmol) in THF (17 mL) was added dropwise to a suspension of NaH (0.658 g, 27.4 mmol, 1.1 equiv) in THF (50 mL) at 0 °C over 25 min. The mixture was stirred at 0 °C for 2 h and then cooled to -78 °C. Methyl iodide (3.711 g, 26.1 mmol, 1.05 equiv) in THF (33 mL) was then added dropwise to the cooled solution over 1 h. The reaction mixture was then allowed to slowly warm to 25 °C and was quenched after 16 h with the addition

of H_2O (150 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to yield 6.608 g (95 %) of **32**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J=8.7 Hz, 1H, Ph), 6.47-6.32 (m, 2H, Ph), 6.02-5.91 (m, 1H, $CH_2CH{=}CH_2$), 5.05-4.97 (m, 2H, $CH_2CH{=}CH_2$), 3.79 (s, 3H, OCH_3), 3.31-3.28 (m, 2H, $CH_2CH{=}CH_2$), 0.99 (s, 9H, 3 CH_3), 0.21 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.97, 155.13, 137.45, 129.83, 121.37, 114.88, 111.44, 103.49, 55.33, 33.59, 25.72, 18.22, -4.40; IR (film) 2956, 2931, 2858, 1607, 1585, 1504, 1469, 1413, 1293, 1256, 1201, 1161, 1122, 1040, 981, 908, 838, 780 cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-propan-1-ol (33). To a solution of **32** (3.460 g, 12.4 mmol) in THF (12.4 mL) maintained at 0 °C was added borane-methylsulfide complex (1.44 mL, 9.5 M, 13.6 mmol, 1.1 equiv) dropwise by syringe. The mixture was allowed to warm to 25 °C and was maintained at that temperature for 3 h. The mixture was once again placed at 0 °C and EtOH (10 mL) was added dropwise. After the addition was complete the solution was allowed to warm to 25 °C. This sequence was repeated with the addition of 3 N aqueous NaOH (4.6 mL) and 30 % aqueous H_2O_2 (19.1 mL). After the final addition was complete, the mixture was maintained at 25 °C for 14 h whereupon it was poured into ice (25 g) and extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide 3.64 g (99 %) of **33** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J=8.6 Hz, 1H, Ph), 6.39-6.35 (m, 2H, Ph), 3.77 (s, 3H, OCH_3), 3.56 (app t, J=6.2 Hz, 2H, CH_2), 2.62 (app t, J=7.2 Hz, 2H, CH_2), 1.83-1.74 (m, 2H, CH_2), 0.96 (s, 9H, 3 CH_3), 0.19 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ

158.11, 155.01, 130.12, 122.69, 111.68, 103.47, 62.32, 55.35, 33.09, 25.71, 25.30, 18.20, -4.39; IR (film) 3317, 2931, 2858, 1608, 1506, 1469, 1289, 1255, 1201, 1160, 1118, 1039, 979, 956, 837, 780 cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-methane sulphonylpropane (34). Methane sulphonylchloride (1.214 g, 0.82 mL, 10.6 mmol, 1.8 equiv) was added dropwise to a solution of **33** (1.740 g, 5.9 mmol) and Et_3N (1.497 g, 2.06 mL, 14.8 mmol, 2.5 equiv) in CH_2Cl_2 (14.8 mL) maintained at 0 °C over 5 min. The reaction mixture was maintained at 0 °C for 3 h at which time it was poured into cold 5 % aqueous HCl (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated to yield 2.19 g (99 %) of **34** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J=8.7 Hz, 1H, Ph), 6.35-6.32 (m, 2H, Ph), 4.18 (app t, J=6.5 Hz, 2H, $CH_2OSO_2CH_3$), 3.75 (s, 3H, OSO_2CH_3), 2.96 (s, 3H, OCH_3), 2.65-2.60 (m, 2H, CH_2), 2.03-1.94 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.17 (C), 155.34 (C), 130.11 (CH), 121.40 (C), 111.33 (CH), 103.45 (CH), 69.84 (CH_2), 55.17 (CH_3), 37.30 (CH_3), 29.23 (CH_2), 26.04 (CH_2), 25.68 (CH_3), 18.18 (C), -4.41 (CH_3); IR (film) 2956, 2932, 2858, 1608, 1584, 1505, 1471, 1414, 1356, 1293, 1257, 1202, 1175, 1119, 1037, 977, 926, 840, 781 cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-propane azide (35). A solution of mesylate **34** (12.061 g, 32.2 mmol), sodium azide (2.301 g, 35.4 mmol, 1.1 equiv), and DMF (161 mL) was maintained at 55 °C for 18 h at which time it was cooled, poured into H_2O (150 mL), and extracted with Et_2O (4 x 50

mL). The combined organics were dried ($MgSO_4$) and concentrated to yield 9.95 g (96 %) of **35** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J=8.7 Hz, 1H, Ph), 6.36-6.33 (m, 2H, Ph), 3.76 (s, 3H, OCH_3), 3.23 (app t, J=6.9 Hz, 2H, CH_2), 2.62-2.57 (m, 2H, CH_2), 1.87-1.76 (m, 2H, CH_2), 0.97 (s, 9H, 3 CH_3), 0.19 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.50 (C), 155.00 (C), 130.03 (CH), 121.99 (C), 111.29 (CH), 103.40 (CH), 55.15 (CH_3), 50.96 (CH_2), 29.01 (CH_2), 26.81 (CH_2), 25.68 (CH_3), 18.18 (C), -4.42 (CH_3); IR (film) 2955, 2931, 2859, 2096, 1609, 1585, 1505, 1469, 1452, 1414, 1390, 1362, 1291, 1254, 1202, 1162, 1116, 1039, 979, 939, 840, 780 cm^{-1}.

3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-propane imine (37). *n*-BuMgBr (0.33 mL, 1.54 M in Et_2O, 0.51 mmol, 1.02 equiv) was added dropwise to a solution containing CuCN (46 mg, 0.51 mmol, 1.02 equiv) and LiCl (43 mg, 1.02 mmol, 2.04 equiv) in THF (1.0 mL) at 0 °C. This resulted in a dark blue solution which was placed at -78 °C. To this mixture was added the imidoyl chloride **24b** (1.0 mmol) in THF (0.5 mL). The mixture was allowed to slowly warm to 25 °C. After 12 h the mixture was quenched with sat. aqueous NH_4Cl (1 mL) and extracted with Et_2O (5 x 2 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$), and concentrated to yield 0.201 g (90 %) of **37** as a slightly yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J=8.7 Hz, 1H, Ph), 6.35-6.32 (m, 2H, Ph), 3.74 (s, 3H, OCH_3), 3.43 (app t, J=6.7 Hz, 2H, CH_2), 2.67-2.62 (m, 2H, CH_2), 2.39-2.34 (m, 2H, CH_2), 1.29 (s, 9H, 3 CH_3), 1.16-1.10 (m, 4H, 2 CH_2), 0.97 (s, 9H, 3 CH_3), 0.93-0.84 (m, 3H, CH_3), 0.18 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.00 (C), 169.00 (C), 158.18 (C), 154.88 (C), 129.92 (CH), 123.16 (C), 111.18 (CH), 103.37 (CH), 55.12 (CH_3),

50.89 (CH_2), 43.57 (C), 31.03 (CH_2), 28.45 (CH_2), 27.75 (CH_3), 27.69 (CH_2), 27.22 (CH_2), 25.68 (CH_3), 22.93 (CH_2), 18.16 (C), 13.69 (CH_3), -4.42 (CH_3).

1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (38). This compound was prepared in a manner analogous to **25a** employing 76 mg (0.25 mmol) of **23b** and 22 mg (0.28 mmol) of acetylchloride. Chromatography (silica gel, ethyl acetate) provided 48 mg (82 %) of **38** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (d, J=9.9 Hz, 1H, C**H**=CH), 6.21 (dd, J=1.4, 9.2 Hz, 1H, CH=C**H**), 5.60 (d, J=1.3 Hz, 1H, CH_3OC=C**H**), 4.17-4.08 (m, 1H, **H**CH-N=C), 3.93-3.82 (m, 1H, HC**H**-N=C), 3.64 (s, 3H, OC**H**$_3$), 2.27 (s, 3H, O=C-C**H**$_3$), 2.15-2.05 (m, 1H, **H**CH-CH_2), 1.83-1.68 (m, 3H, HC**H**-C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.77, 187.13, 177.65, 163.02, 144.72, 128.17, 102.00, 55.80, 50.10, 45.55, 34.29, 25.24, 18.17; IR (film) 2940, 1703, 1659, 1637, 1592, 1456, 1391, 1360, 1269, 1224, 1180, 1107, 1059, 1015, 977, 928, 854 cm^{-1}; MS (EI) 233, 191, 164, 137, 107, 77, 43; high resolution mass spectrum calcd. for $C_{13}H_{15}NO_3$; M^+ =233.1052. Found: M^+ =233.1047.

1- Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (40). The title compound was prepared in a manner analogous to **25a** but employing 0.153 g (0.50 mmol) of **23b** and 0.120 g (0.55 mmol) of phenylsulphonylacetylchloride. Chromatography (silica gel, ethyl acetate) provided 0.103 g (55 %) of **40** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2H, Ph), 7.67-7.62 (m, 1H, Ph), 7.56-7.50 (m, 2H, Ph), 6.49 (d, J=10.0 Hz, 1H, C**H**=CH), 6.24 (d, J=9.9 Hz, 1H, CH=C**H**), 5.60 (s, 1H, CH_3O-C=C**H**), 4.94 (d, J=13.0 Hz, 1H, O=C-C**H**H-SO_2Ph), 4.48 (d, J=13.0 Hz, 1H,

O=C-CH**H**-SO_2Ph), 4.13-4.07 (m, 1H, **H**CH-C=N), 3.90-3.79 (m, 1H, HC**H**-C=N), 3.62 (s, 3H, OC**H**$_3$), 2.14-2.02 (m, 1H, **H**CH-CH_2), 1.85-1.69 (m, 3H, HC**H**-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.16, 187.04, 177.00, 162.14, 143.75, 139.10, 134.08, 129.14, 128.80, 128.34, 102.05, 60.35, 55.99, 50.46, 45.23, 33.84, 17.95; IR (film) 2939, 1709, 1656, 1635, 1591, 1448, 1392, 1363, 1322, 1225, 1155, 1085, 1040, 1017, 954, 855, 812, 760 cm^{-1}; MS (EI) 373, 191, 164, 137, 107, 90, 77, 77, 51; high resolution mass spectrum calcd. for $C_{19}H_{19}NO_5S$; M^+ =373.0984. Found: M^+ =373.0987.

1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (42). This compound was prepared in a manner similar to **25** utilizing 1.527 g (5.0 mmol) of **23b** and 1.027 g (5.5 mmol) of phenylthioacetylchloride. Chromatography (50 % ethyl acetate/CH_2Cl_2) afforded 1.71 g (83 %) of **42** as a thick brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.12 (m, 5H, Ph), 6.50 (d, J=9.9 Hz, 1H, C**H**=CH), 6.14 (d, J=9.8 Hz, 1H, CH=C**H**), 5.53 (s, 1H, CH_3O-C=C**H**), 4.10-4.00 (m, 1H, **H**CH-C=N), 4.05 (s, 2H, O=C-C**H**$_2$-SPh), 3.89-3.60 (m, 1H, **H**CH-C=N), 3.47 (s, 3H, OC**H**$_3$), 2.12-2.05 (m, 1H, **H**CH-CH_2), 1.80-1.68 (m, 3H, HC**H**-C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.75, 186.92, 177.11, 161.94, 144.10, 135.40, 129.25, 128.79, 128.39, 126.42, 102.00, 55.65, 50.00, 45.50, 38.37, 33.91, 18.00; IR (film) 2927, 2855, 1768, 1702, 1658, 1636, 1591, 1481, 1439, 1362, 1284, 1223, 1178, 1120, 1089, 1022, 955, 939, 853, 742 cm^{-1}; MS (EI) 341, 232, 191, 164, 150, 137, 123, 110, 77, 65, 51, 45; high resolution mass spectrum calcd. for $C_{19}H_{19}NO_3S$: M^+ =341.1086. Found: M^+ =341.1088.

Phenylthio tricycle (43). To a slurry of NaH (9 mg, 0.23 mmol, 1.1 equiv) in DMF (1.4 mL) at 0 °C was added a solution of **42** (72 mg, 0.21 mmol) in DMF (2.8 mL) dropwise over 10 min. This mixture was allowed to rise to 25 °C over several hours. After 12 h the mixture was cooled to -78 °C and SEM-Cl (39 mg, 40.9 mL, 0.23 mmol, 1.1 equiv) was added over 1 min. The reaction mixture was allowed to warm to 25 °C over 2 h whereupon it was poured into H_2O (10 mL), extracted with ethyl acetate (4 x 5 mL), dried ($MgSO_4$), and concentrated to yield 95 mg (96 %) of **43** as a thick brown paste. As the purity of this compound was 100 % by NMR chromatography was not utilized. This compound was found to deteriorate over a short amount of time if not stored at -20 °C in a matrix of benzene. If chromatography was needed it was performed quickly on Florisil (50 % ethyl acetate/CH_2Cl_2). Silica gel and alumina were found to be incompatible with this compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (d, J=6.1 Hz, 1H, O-C**H**H-O), 5.31 (s, 1H, CH_3O-C=C**H**), 5.06 (d, J=5.7 Hz, 1H, O-CH**H**-O), 3.85-3.73 (m, 3H, O-CH_2-C**H**H, C**H**$_2$-N=C), 3.62 (s, 3H, OC**H**$_3$), 3.58-3.49 (m, 1H, O-CH_2-CH**H**), 3.04 (d, J=5.8 Hz, 1H, C**H**-CH_2), 2.61 (d, J=17.8 Hz, 1H, CH-CHH), 2.30 (dd, J=17.7, 6.2 Hz, 1H, CH-CH**H**), 2.11-2.05 (m, 1H, **H**CH), 1.94-1.85 (m, 2H, C**H**$_2$), 1.55-1.45 (m, 1H, HC**H**), 0.86-0.77 (m, 2H, C**H**$_2$Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.12 (C), 178.24 (C), 166.90 (C), 154.73 (C), 133.05 (C), 130.05 (CH), 129.11 (CH), 127.82 (C), 126.90 (CH), 101.65 (CH), 93.37 (CH_2), 66.44 (CH_2), 56.09 (CH_3), 48.66 (C), 48.54 (CH_2), 46.48 (CH), 32.95 (CH_2), 28.32 (CH_2), 19.91 (CH_2), 18.15 (CH^2), -1.45 (CH_3); IR (film) 2950, 1767, 1660, 1603, 1477, 1439, 1409, 1346, 1248, 1248, 1217, 1148, 1100, 1038, 1023, 947, 859, 835, 743, 692 cm^{-1}; MS (EI) 471, 398, 370, 336, 304, 232, 110, 91, 73, 59; high resolution mass spectrum calcd. for $C_{25}H_{31}NO_4SSi$:

M+ =471.1900. Found: M^+ =471.1904.

***N*-Methyl-2-phenyl-pyrrolidine (45).** To a solution of SmI_2 (15 mL, 0.1 M in THF, 1.5 mmol, 3.0 equiv) at 25 °C was added $Fe(DBM)_3$ in THF (10 mL) dropwise. The resulting purple solution was then placed at -78 °C and the iminium salt **44** (0.5 mmol) in THF (5 mL) was added dropwise. This mixture was allowed to warm to 25 °C over 4 h whereupon it was quenched with sat. aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried ($MgSO_4$) and concentrated. Chromatography (silica gel, 20 % ethyl acetate/hexane) provided 42 mg of **45** in 52 % unoptomized yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H, Ph), 4.21 (s, 1H, NC**H**), 2.75-2.70 (m, 2H, C**H**$_2$), 2.39-2.18 (m, 2H, C**H**$_2$), 1.93 (s, 3H, C**H**$_3$), 1.69-1.55 (m, 2H, C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.37 (CH), 128.60 (C), 127.49 (CH), 126.82 (CH), 68.70 (CH), 54.11 (CH_2), 36.10 (CH_3), 31.46 (CH_2), 6.21 (CH_2).

1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (51). This compound was prepared in a manner analogous to **25** utilizing 0.305 g (1.0 mmol) of **23b** and 137 mg (1.1 mmol) of methylthioacetylchloride. Chromatograpy (Florisil, 50 % ethyl acetate/CH_2Cl_2) provided 0.235 g (84 %) of **51** as a thick brown paste: ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, J=9.9 Hz, 1H, C**H**=CH), 6.23 (dd, J=9.9, 1.6 Hz, 1H, C**H**=CH), 5.63 (d, J=1.2 Hz, 1H, CH_3O-C=C**H**), 4.15-4.07 (m, 1H, **H**CH-N=C), 3.95-3.84 (m, 1H, HC**H**-N=C), 3.67 (s, 3H, OC**H**$_3$), 3.62 (d, J=13.2 Hz, 1H, O=C-CH**H**-SCH_3), 3.47 (d, J=13.2 Hz, 1H, O=C-CH**H**-SCH_3), 2.18-2.09 (m, 1H, **H**CH=CH_2), 1.97 (s, 3H, SC**H**$_3$), 1.86-1.73 (m,

3H, HC**H**=C**H**$_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.74 (C), 187.34 (C), 177.78 (C), 161.71 (C), 144.61 (CH), 128.33 (CH), 101.69 (CH), 55.85 (CH_3), 50.04 (CH_2), 45.44 (C), 36.68 (CH_2), 33.67 (CH_2), 17.95 (CH_2), 15.64 (CH_3); IR (film) 3365, 2958, 2930, 2857, 1693, 1658, 1637, 1592, 1539, 1504, 1464, 1392, 1362, 1324, 1286, 1260, 1224, 1179, 1105, 1017, 980, 945, 841, 798 cm^{-1}; MS (EI) 279, 191, 164, 137, 77, 61; high resolution mass spectrum calcd. for $C_{14}H_{17}NO_3S$: M+ =279.0929. Found: M+ =279.0929.

Methylthio tricycle (52). This compound was prepared in a manner analogous to **43** employing 0.127 g (0.45 mmol) of **51**. Concentration of solvents provided 0.180 g (98 %) of **52** as a thick brown paste. This compound was also found to deteriorate over a short amount of time if not stored at -20 °C in a matrix of benzene. If chromatography was needed it was performed quickly on Florisil (50 % ethyl acetate/CH_2Cl_2). Silica gel and alumina were found to be incompatible with this compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, J=5.9 Hz, 1H, O-C**H**H-O), 5.33 (s, 1H, CH_3O-C=C**H**), 5.04 (d, J=5.9 Hz, 1H, O-CH**H**-O), 3.78-3.67 (m, 3H, O-C**H**H-CH_2), 3.63 (s, 3H, OC**H**$_3$), 3.60-3.55 (m, 1H, O-CH**H**-CH_2), 3.03 (d, J=5.5 Hz, 1H, C**H**-CH_2), 2.84 (d, J=17.7 Hz, 1H, CH-C**H**H), 2.58 (dd, J=17.7, 6.3 Hz, 1H, CH-CH**H**), 2.46 (s, 3H, SC**H**$_3$), 2.13-1.86 (m, 3H, **H**CH), 1.58-1.40 (m, 1H, HC**H**), 0.92-0.79 (m, 2H, C**H**$_2$Si(CH_3)$_3$), -0.03 (s, 9H, 3 C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.11 (C), 178.66 (C), 166.77 (C), 150.87 (C), 131.56 (C), 101.46 (CH), 93.49 (CH_2), 66.56 (CH_2), 56.03 (CH_3), 48.29 (CH_2), 47.43 (CH), 47.36 (C), 33.32 (CH_2), 28.13 (CH_2), 19.99 (CH_2), 18.21 (CH_2), 15.41 (CH_3), -1.44 (CH_3); IR (film) 2949, 1660, 1603, 1506, 1438, 1416, 1346, 1249, 1217, 1148, 1100, 1039, 1007, 948, 859, 836, 758 cm^{-1}; MS

(EI) 409, 366, 336, 308, 231, 117, 73, 57, 43; high resolution mass spectrum cacld. for $C_{20}H_{31}NO_4SSi$: M^+ =409.1743. Found: M^+ =409.1743.

REFERENCES

REFERENCES

1. Jolly, R.S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536.

2. Kelly, T.R.; Liu, H.-t. *J. Am. Chem. Soc.* **1985**, *107*, 4998.

3. Martin, S.F.; Benage, B.; Geraci, L.S.; Hunter, J.E. Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161.

4. Kleinman, E.; Heathcock, C.H. *Tetrahedron Lett.* **1979**, 4125.

5. Czerwinski, K.M.; Deng, L.; Cook, J.M. *Tetrahedron Lett.* **1992**, 4721.

6. a) Belleau, B. *J. Am. Chem. Soc.* **1948**, *70*, 3569.
   b) Mondron, A. *Angew. Chem.* **1956**, *68*, 578.

7. Schoemaker, H.E.; Speckamp, W.N. *Tetrahedron Lett.* **1982**, 3807.

8. Nossin, P.M.M.; Hamersma, J.A.M.; Speckamp, W.N. *Tetrahedron Lett.* **1982**, 3807.

9. Hart, D.J.; Yang, T.-K. *J. Chem. Soc. Chem. Commun.* **1983**, 135.

10. Overman, L.E.; Kakimoto, M.-a.; Okazaki, M.E.; Meier, G.P. *J. Am. Chem. Soc.* **1983**, *105*, 6622. This reaction was originally described by Geissman: Horowitz, R.M.; Geissman, T.A. *J. Am. Chem. Soc.* **1950**, *72*, 1518.

11. Knight, S.D.; Overman, L.E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

12. Overman, L.E. *Acc. Chem. Res.* **1992**, *25*, 352.

13. Flann, C.J.; Overman. L.E. *J. Am. Chem. Soc.* **1987**, *109*, 6115.

14. Wasserman, H.H.; Cook, J.D.; Vu, C.B. *J. Org. Chem.* **1990**, *55*, 1701.

15. Wasserman, H.H.; Kuo, G.-H. *Tetrahedron* **1992**, *48*, 7071.

16. Wasserman, H.H.; Henke, S.L.; Nakanishi, E.; Schulte, G. *J. Org. Chem.* **1992**, *57*, 2641.

17. Heathcock, C.H.; Hansen, M.M.; Ruggeri, R.B.; Kath, J.C. *J. Org. Chem.* **1992**, *57*, 2544.

18. a) Bischler, A.; Naperalski, B. *Ber.* **1893**, *26*, 1903.

b) Whaley. W.M.; Govindachari, T.R. "Organic Reactions," Vol. 6, R. Adams, Ed.; p. 74, John Wiley and Sons, New York, **1951**.

19. a) Lora-Tamayo, M.; Madronero, R. *Chem. & Ind.* **1959**, 657.
b) Lora-Tamayo, M.; Madronero, R.; Gracian, D.; Gometz-Parra, V. *Tetrahedron Suppl. 8 Part 1,* 1966, 305.

20. Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, 94, 1116.

21. a) Westling, M.; Livinghouse, T. *Tetrahedron Lett.* **1985**, 5389.
b) Westling, M.; Smith, R.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590.

22. Westling, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590.

23. Luedtke, G.; Westling, M.; Livinghouse, T. *Tetrahedron* **1992**, *48*, 2209.

24. Lee, C.H.; Westling, M.; Livinghouse, T.; Williams, A.C. J. *Am. Chem. Soc.* **1992**, *114*, 4089.

25. Braekman, J.C.; Nyembo, L.; Symoens, J.J. *Phytochemistry* **1980**, *19*, 803.

26. Blumenkopf, T.A.; Heathcock, C.H. "Aklaloids," S.W. Pelletier, Ed.; p. 185, John Wiley and Sons, New York, **1985**.

27. Yu, C.; Shen, W.; Han, J.; Chen, Y.; Zhu, Y. *Yaoxue Xuebao* **1982**, *17*, 795; *CA:* **98**: 40466.

28. Ayer, W.A.; Kasitu, G.C. *Can. J. Chem.* **1989**, *67*, 1077.

29. Marshall, W.D.; Nguyen, T.T.; MacLean, N.B.; Spenser, I.D. *Can. J. Chem.* **1975**, *53*, 41.

30. Inubushi, Y.; Ishii, H.; Yasui, B.; Harayama, T. *Tetrahedron Lett.* **1966**, 1551.

31. Blumenkopf, T.A.; Heathcock, C.H. "Alkaloids," S.W. Pelletier, Ed,; p. 230, John Wiley and Sons, New York, **1985**.

32. Stork, G.; Kretchmer, A.; Schlessinger, R.H. *J. Am. Chem. Soc.* **1968**, *90*, 1648.

33. Ayer, W.A.; Bowman, W.R.; Joseph, T.C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1647.

34. Harayama, T.; Ohtani, M.; Oki, M.; Inubushi, Y. *J. Chem. Soc. Chem Commun.* **1974**, 827; *Chem. Pharm. Bull.* **1975**, *23*, 1511.

35. Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, 4307; *Chem. Pharm. Bull.* **1980**, *28*, 2394.

36. Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

37. Wadsworth, W.S. Jr. *Org. React.* **1977**, *25*, 73.

38. DiBiase, S.A.; Lipisko, B.A.; Haag, A.; Wolak, R.A.; Gokel, G.W. *J. Org. Chem.* **1979**, *44*, 4640.

39. Ishibashi, H.; So, T.S.; Sato, T.; Kuroda, K.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 762.

40. Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

41. Ohsawa, T.; Ihara, M.; Fukaumoto, k.; Kametani, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644.

42. Overman. L.E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229.

43. Narasimhan, N. *Diss. Abst. Inter. B* **1983**, *44*, 804.

44. Ueno, Y.; Ohta, M.; Okawara, M. *Tetrahedron Lett.* **1982**, 2577.

45. Goswami, R.; Corcoran, D.E. *Tetrahedron Lett.* **1982**, 1463.

46. Stork, G.; Taber, D.F.; Marx, M. *Tetrahedron Lett.* **1978**, 2445.

47. Molander, G.A. *Chem. Rev.* **1992**, *92*, 29.

48. Martin, S.F.; Yang, C.-P.; Laswell, W.L.; Rüger, H. *Tetrahedron Lett.* **1988**, 6685.

49. Molander, G.A.; Etter, J.B. *Synth. Commun.* **1987**, *17*, 901.

50. Molander, G.A.; Etter, J.B. *J. Org. Chem.* **1986**, *51*, 1778.

51. Molander, G.A.; McKie, J.A. *J. Org. Chem.* **1991**, *56*, 4112.

52. Curran, D.P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106.

53. Still, W.C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.

54. Boger, D.L.; Wysocki, R.J. *J. Org. Chem.* **1989**, *54*, 1238.

55. Stork, G.; Baine, N.H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

56. Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801.

57. Tiner-Harding, T.; Ullrich, J.W.; Chiu, F.-T.; Chen, S.-f. *J. Org. Chem.* **1982**, *47*, 3362.

58. Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.

59. Trost, B.M.; Curran, D.P. *Tetrahedron Lett.* **1981**, 5023.

APPENDIX

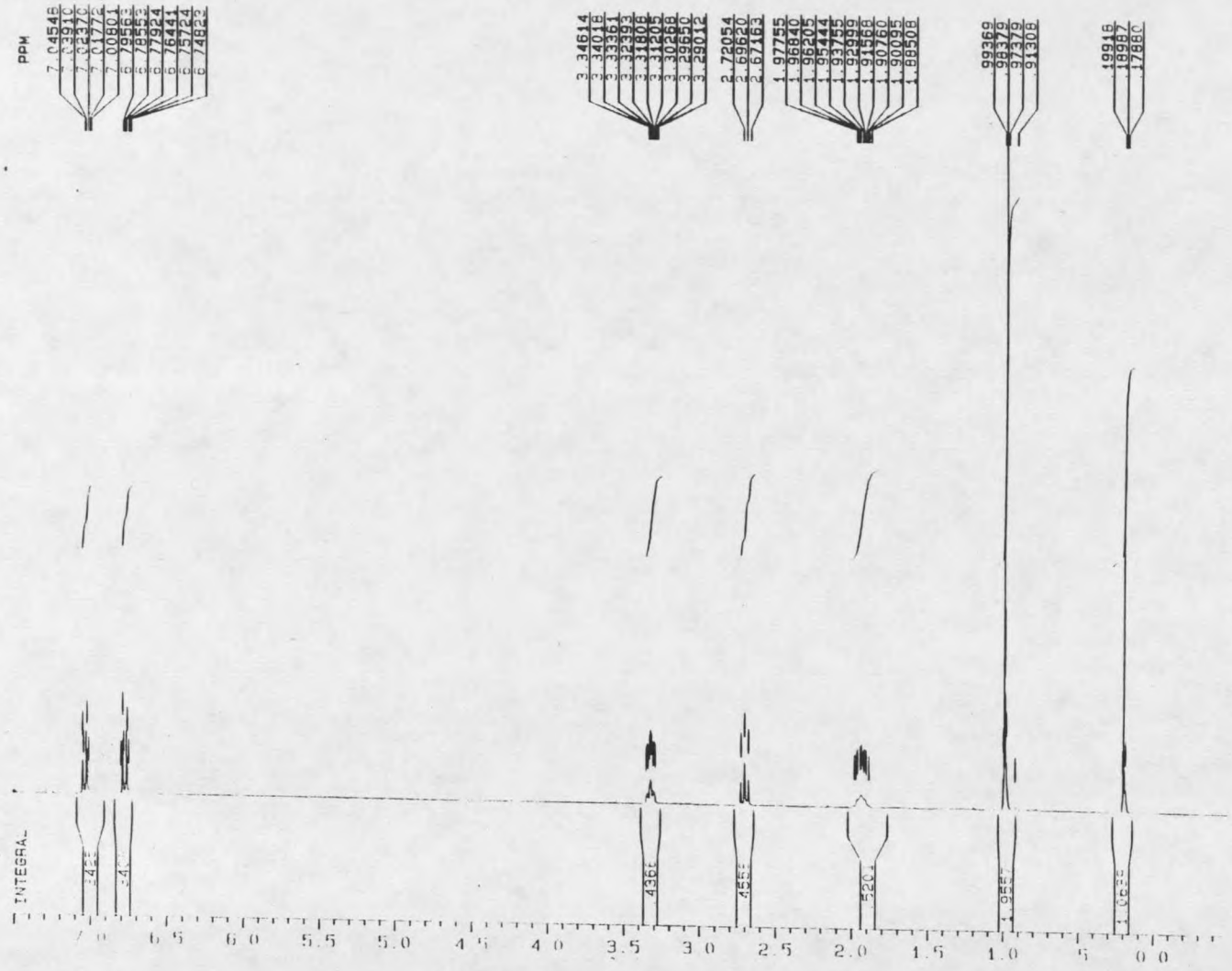


Figure 5. ^{1}H NMR Spectrum of 3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23a**).

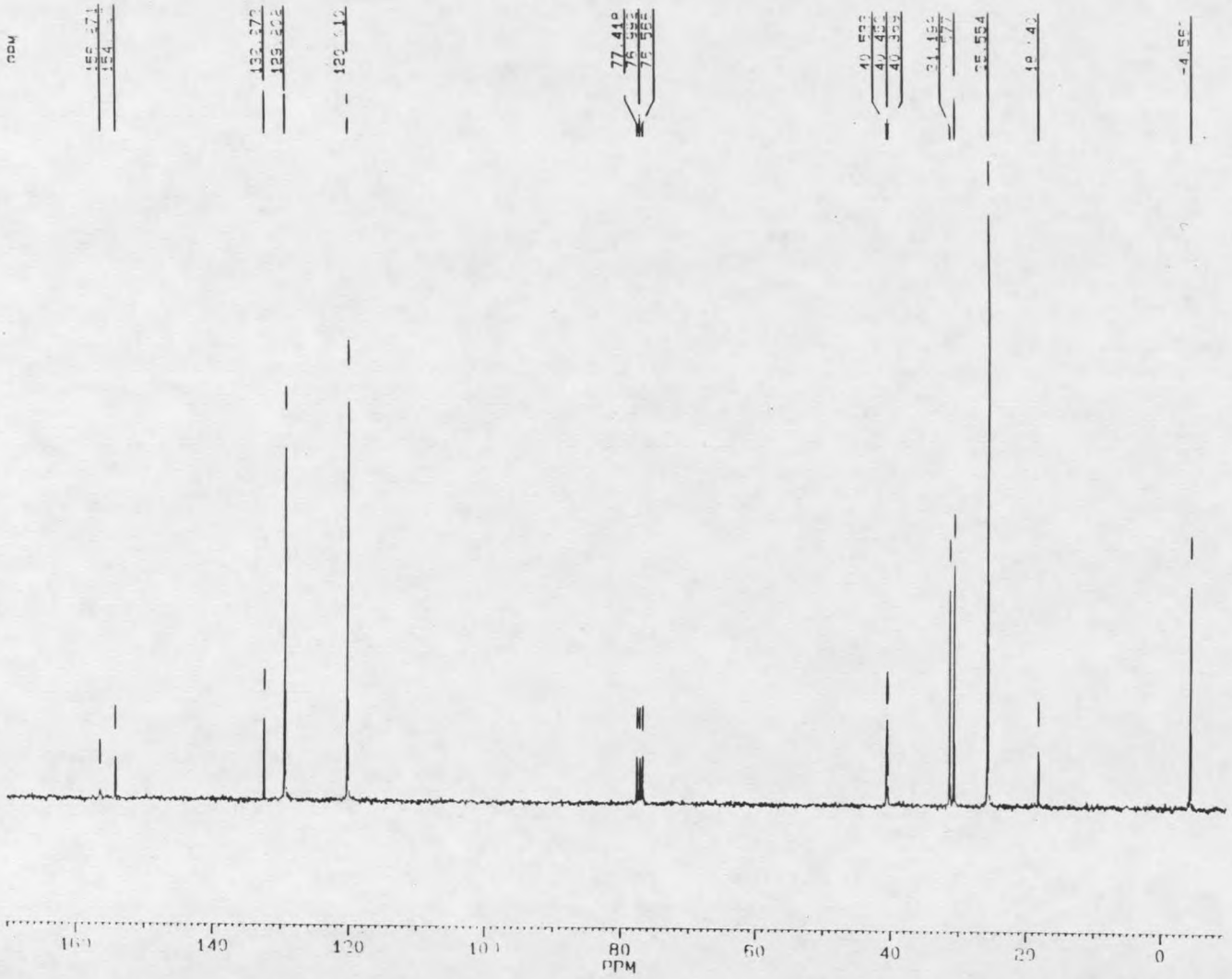


Figure 6. ^{13}C NMR Spectrum of 3-(4-*t*-Butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile **(23a)**.

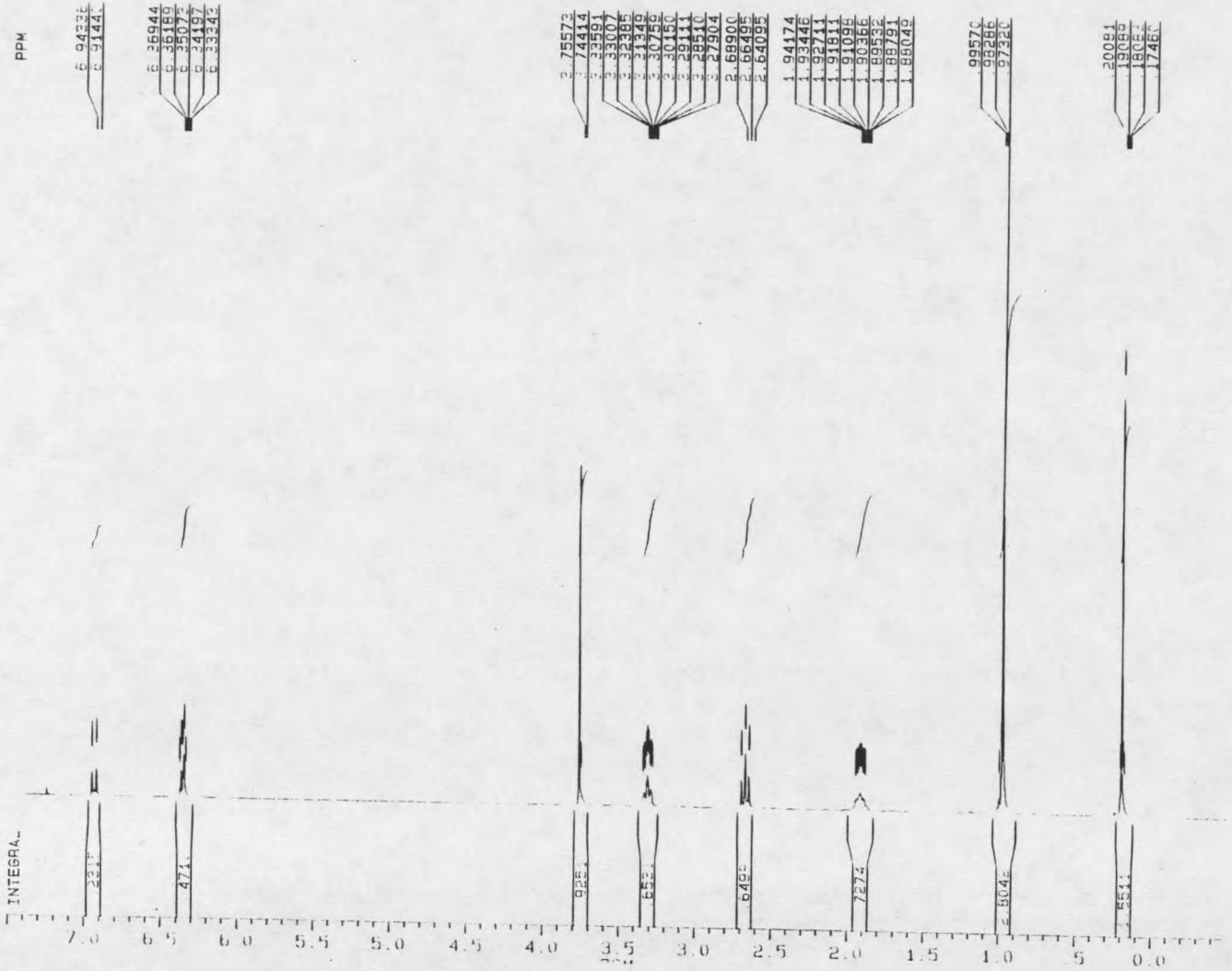


Figure 7. ^{1}H NMR Spectrum of 3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23b**).

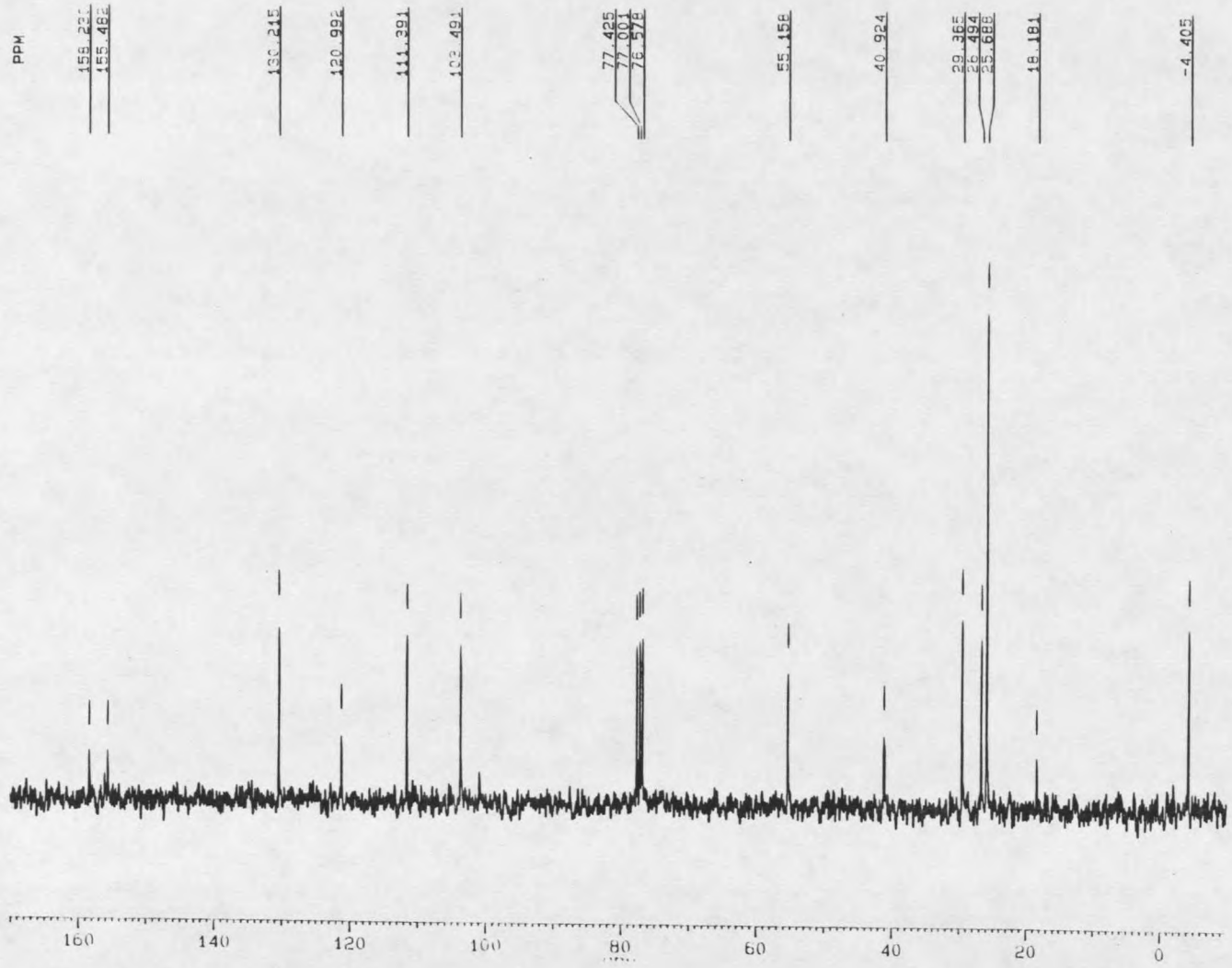


Figure 8. ^{13}C NMR Spectrum of 3-(2-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23b**).

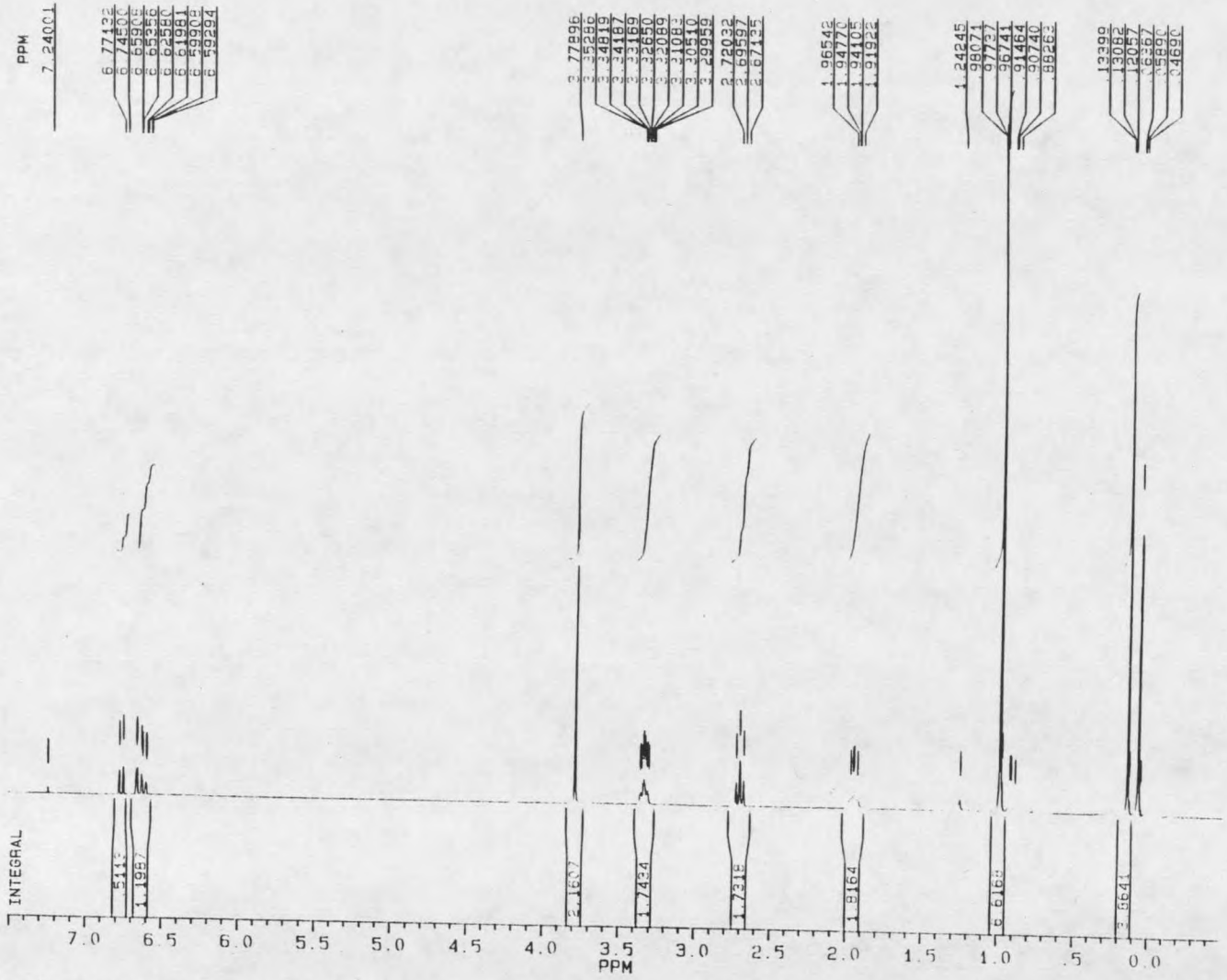


Figure 9. ^{1}H NMR Spectrum of 3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23c**).

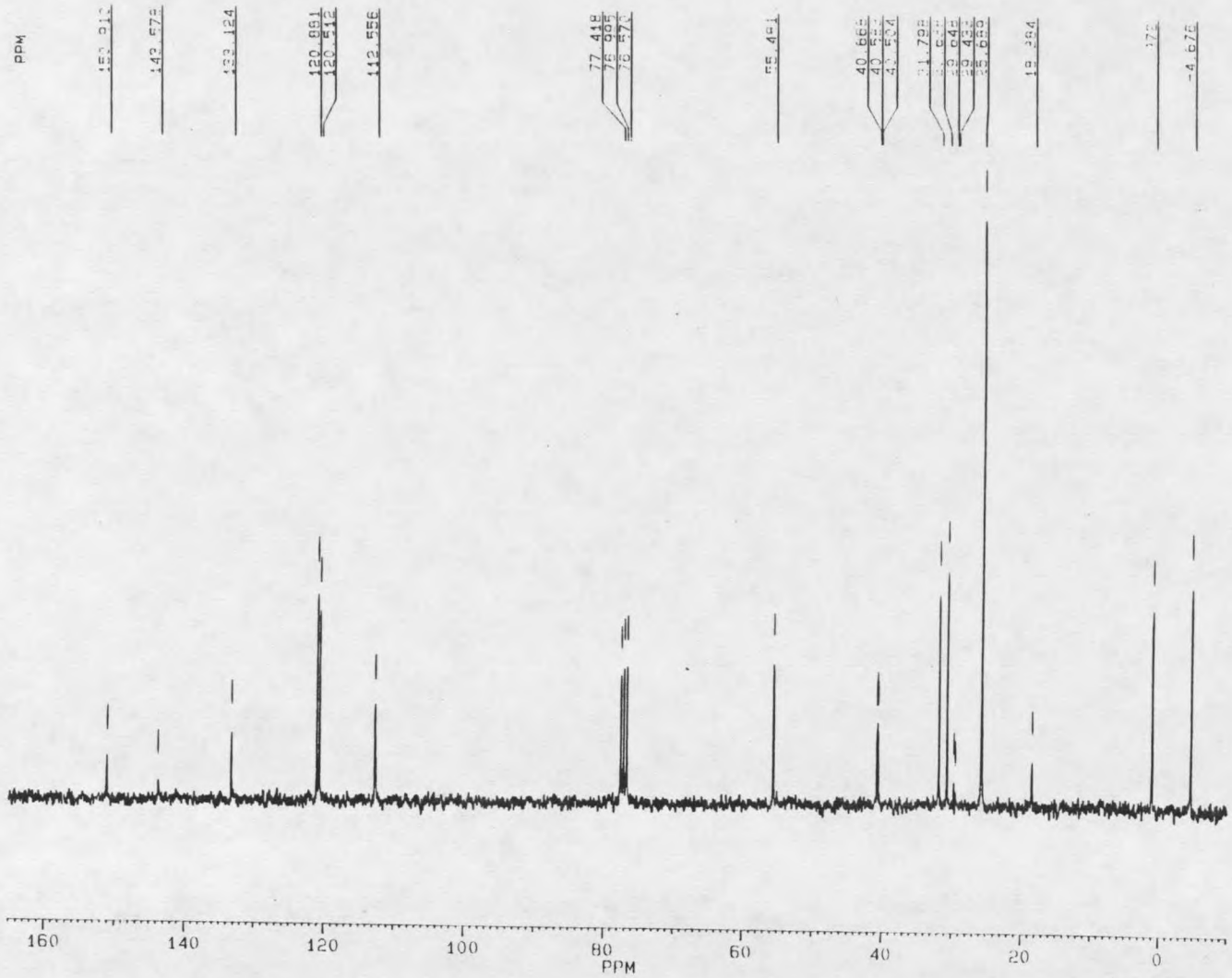


Figure 10. ^{13}C NMR Spectrum of 3-(3-Methoxy-4-*t*-butyldimethylsilyloxyphenyl)-prop-1-ylisonitrile (**23c**).

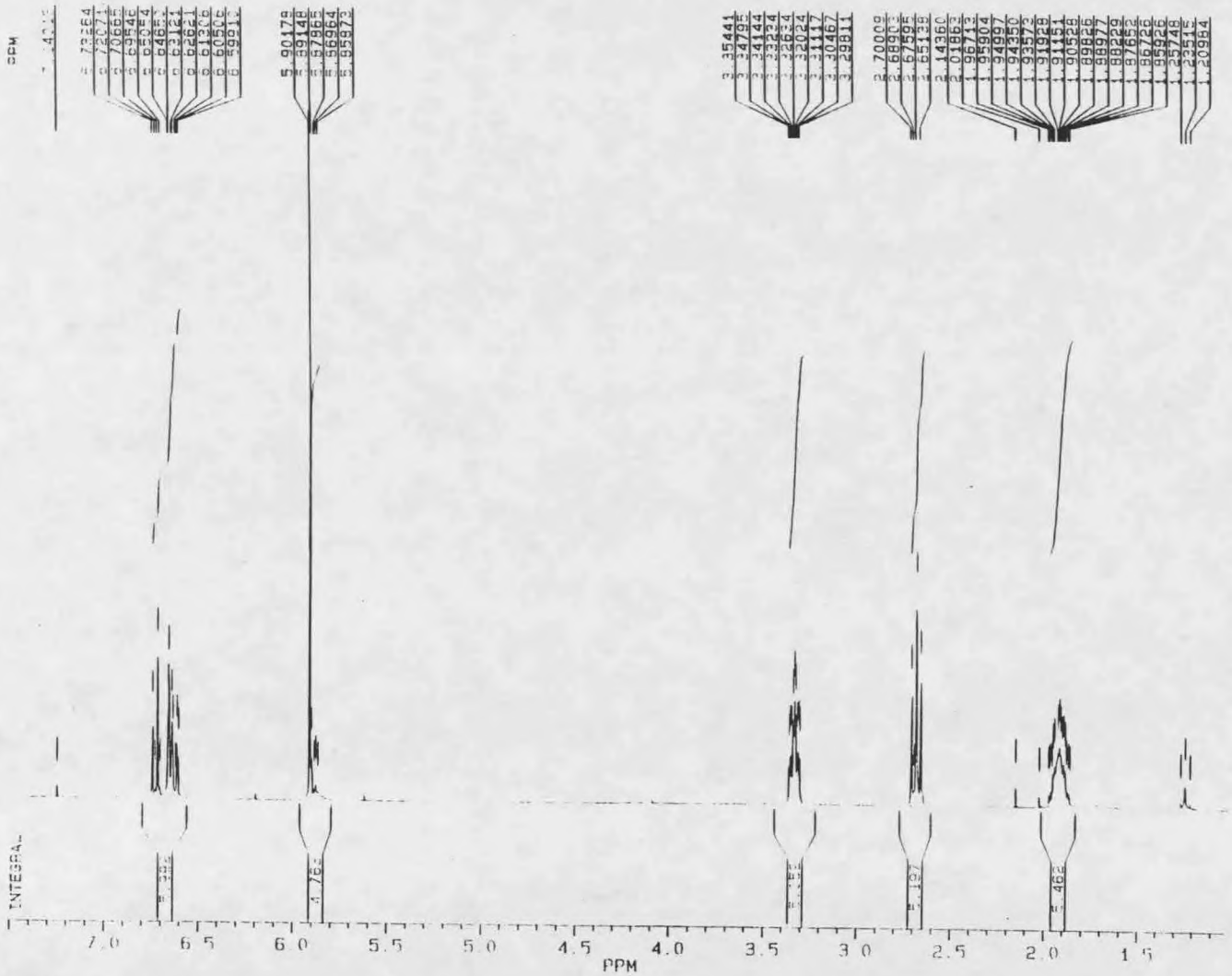


Figure 11. ^{1}H NMR Spectrum of 3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (**23d**).

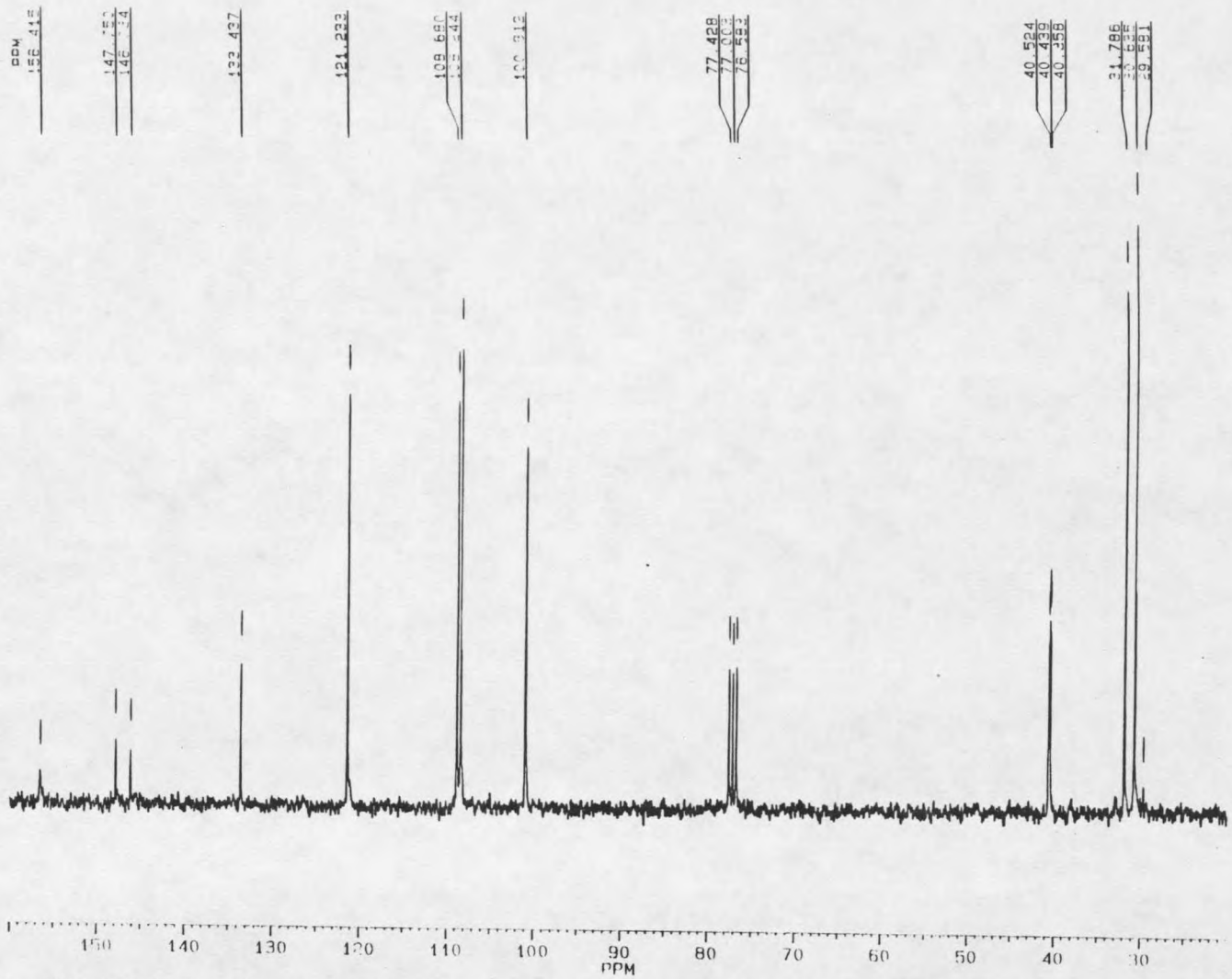


Figure 12. ^{13}C NMR Spectrum of 3-(3,4-Methylenedioxyphenyl)-prop-1-ylisonitrile (**23d**).

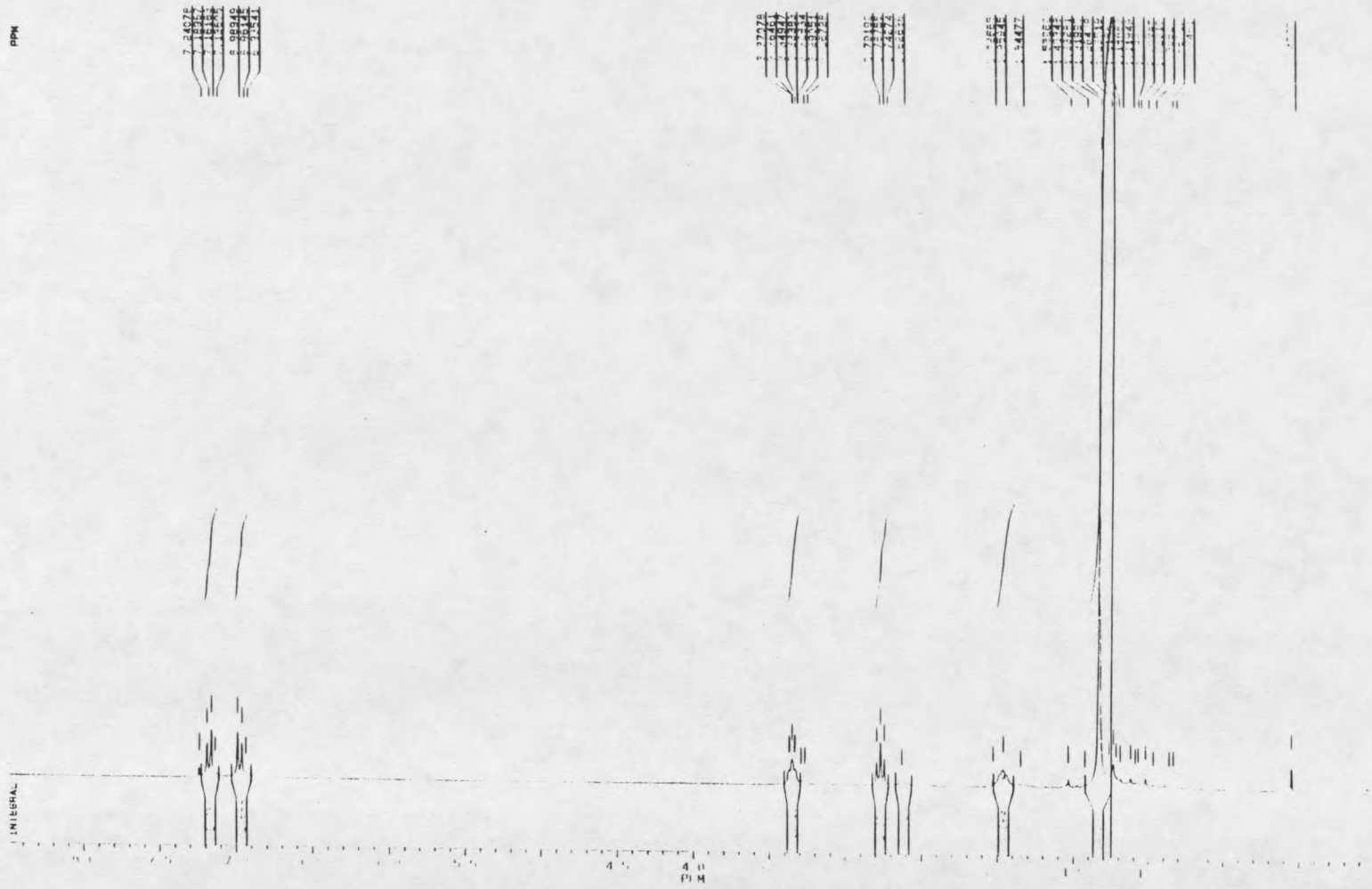


Figure 13. ^{1}H NMR Spectrum of 7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25a**).

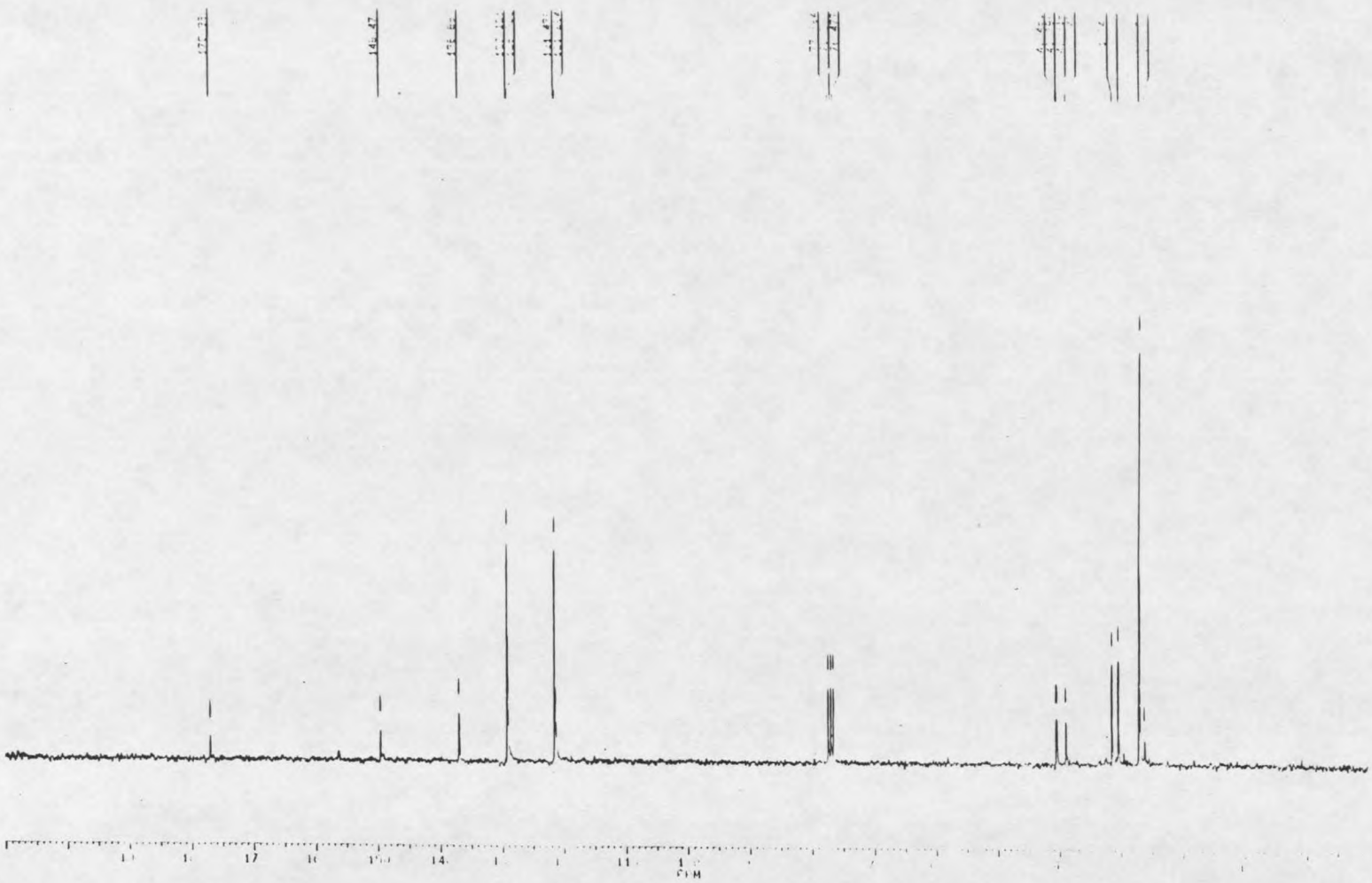


Figure 14. ^{13}C NMR Spectrum of 7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25a**).

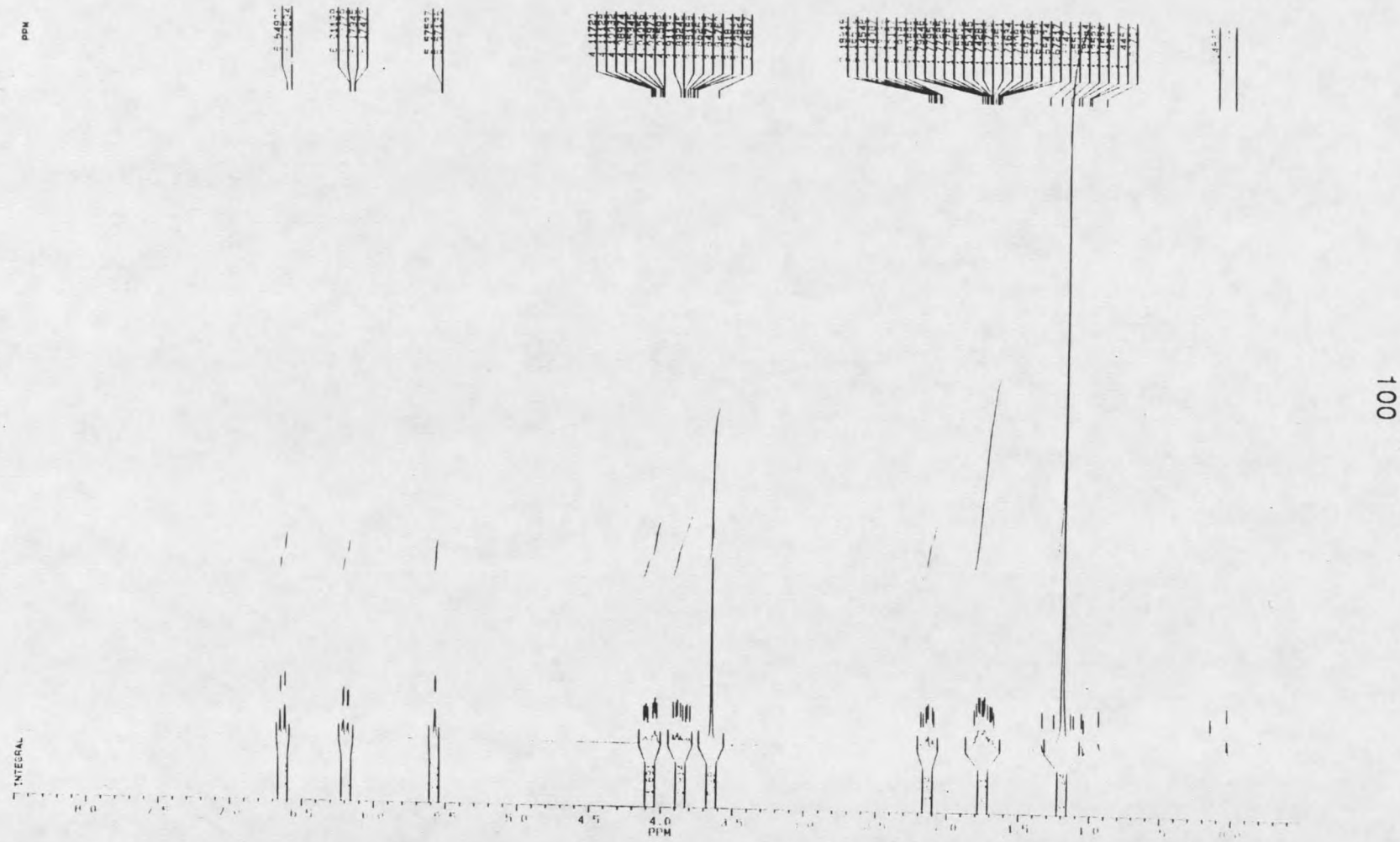


Figure 15. ^{1}H NMR Spectrum of 1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25b**).

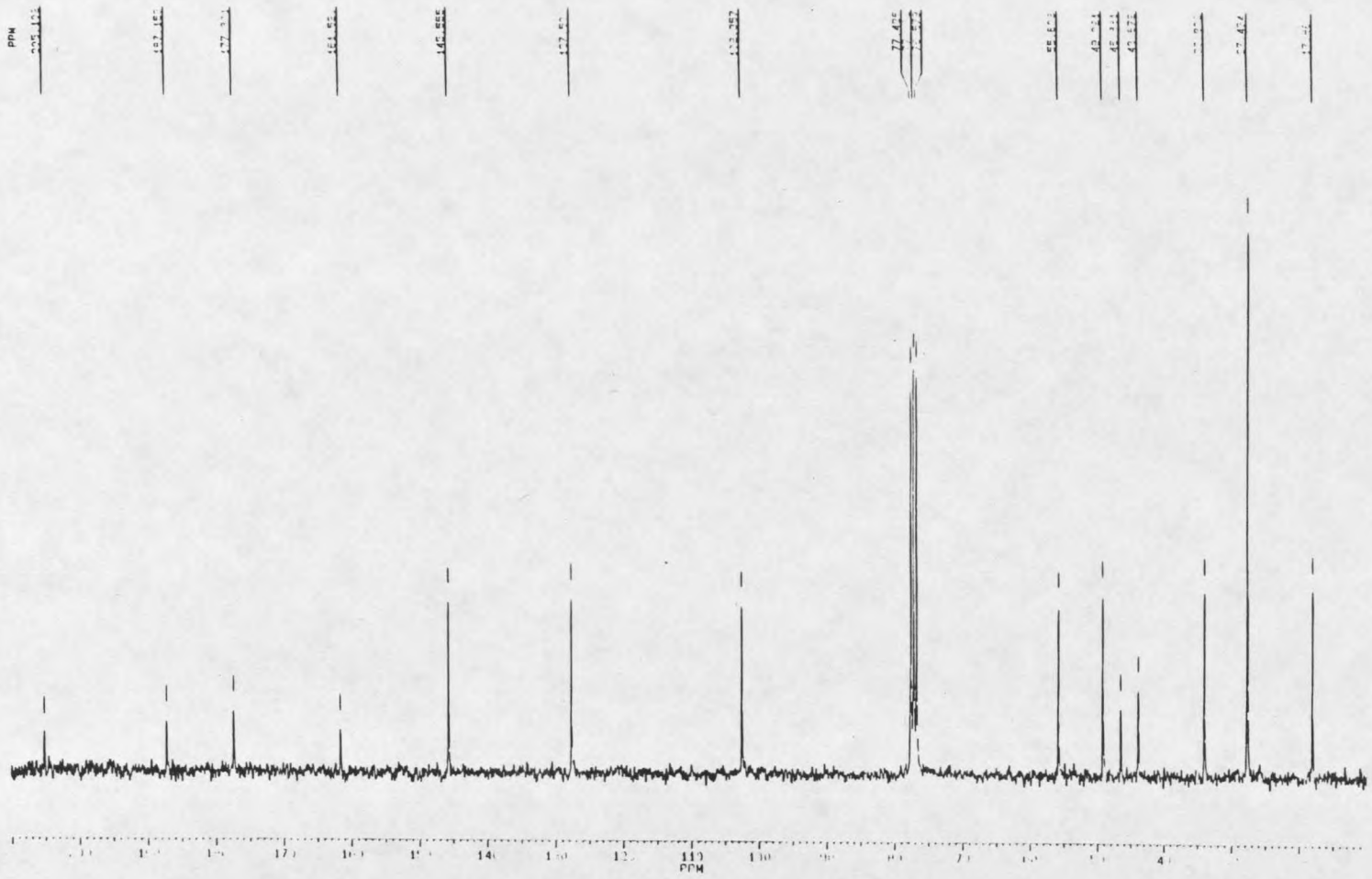


Figure 16. ^{13}C NMR Spectrum of 1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**25b**).

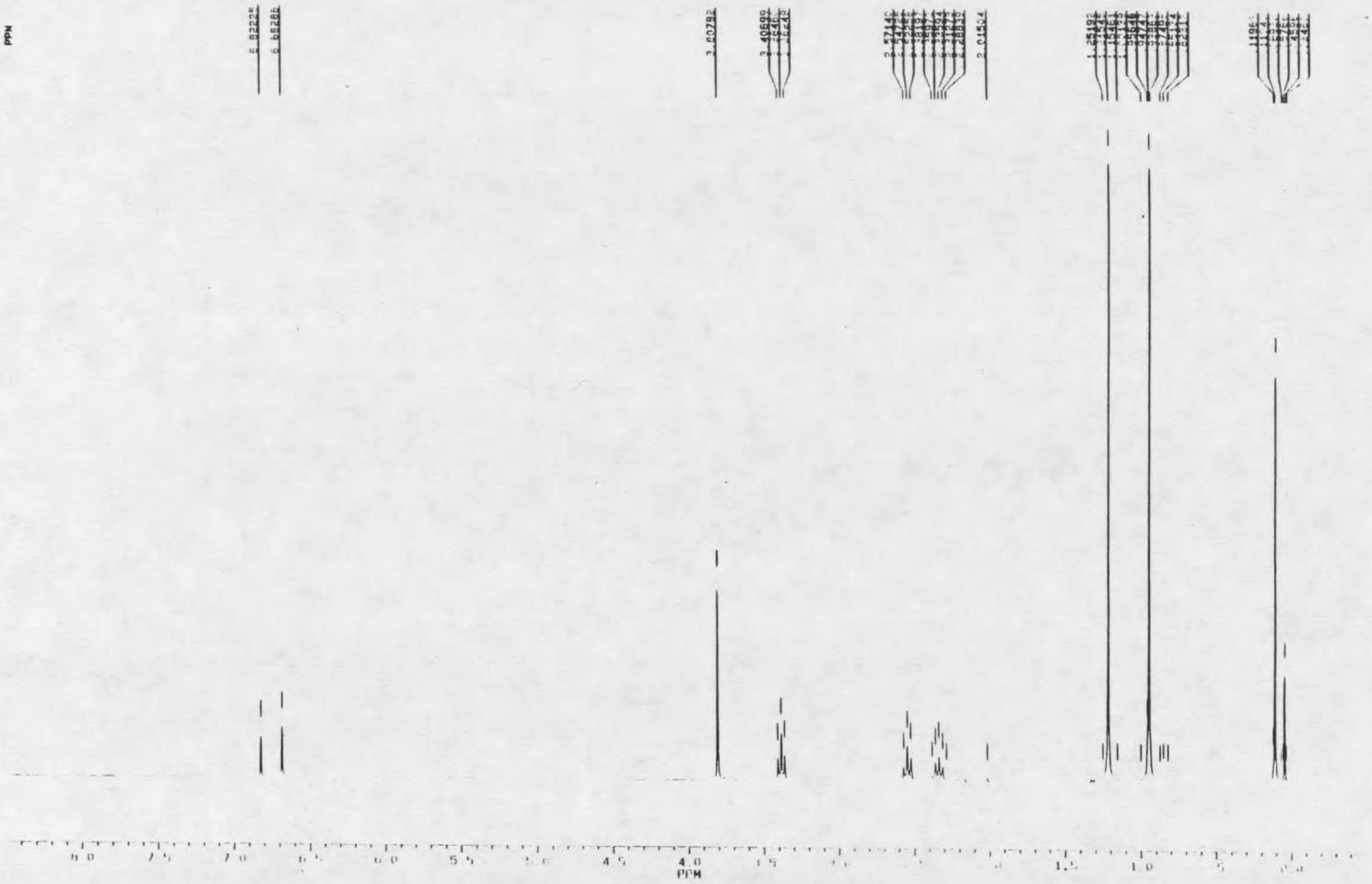


Figure 17. ^{1}H NMR Spectrum of 1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (**25c**).

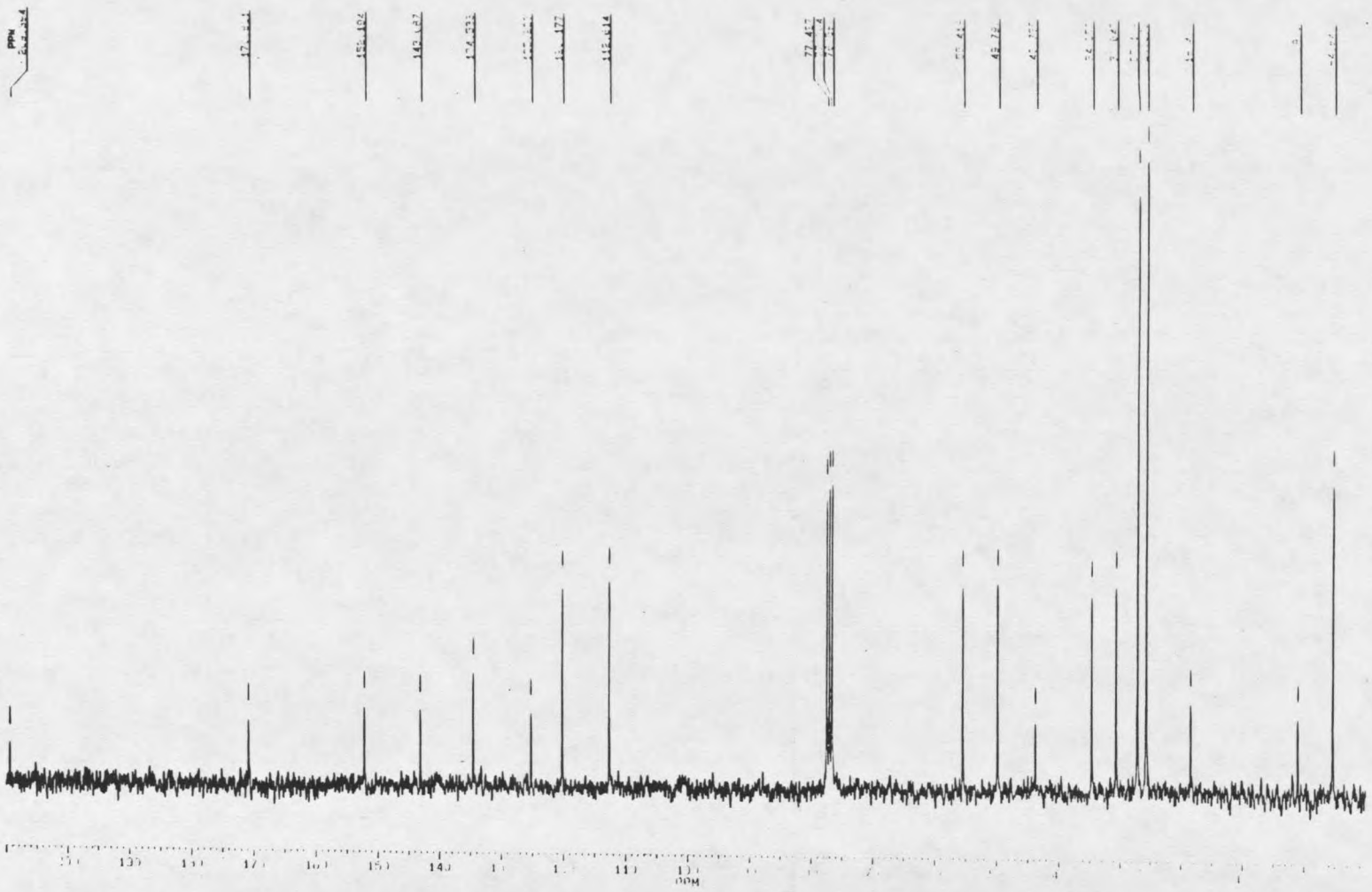


Figure 18. ^{13}C NMR Spectrum of 1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (**25c**).

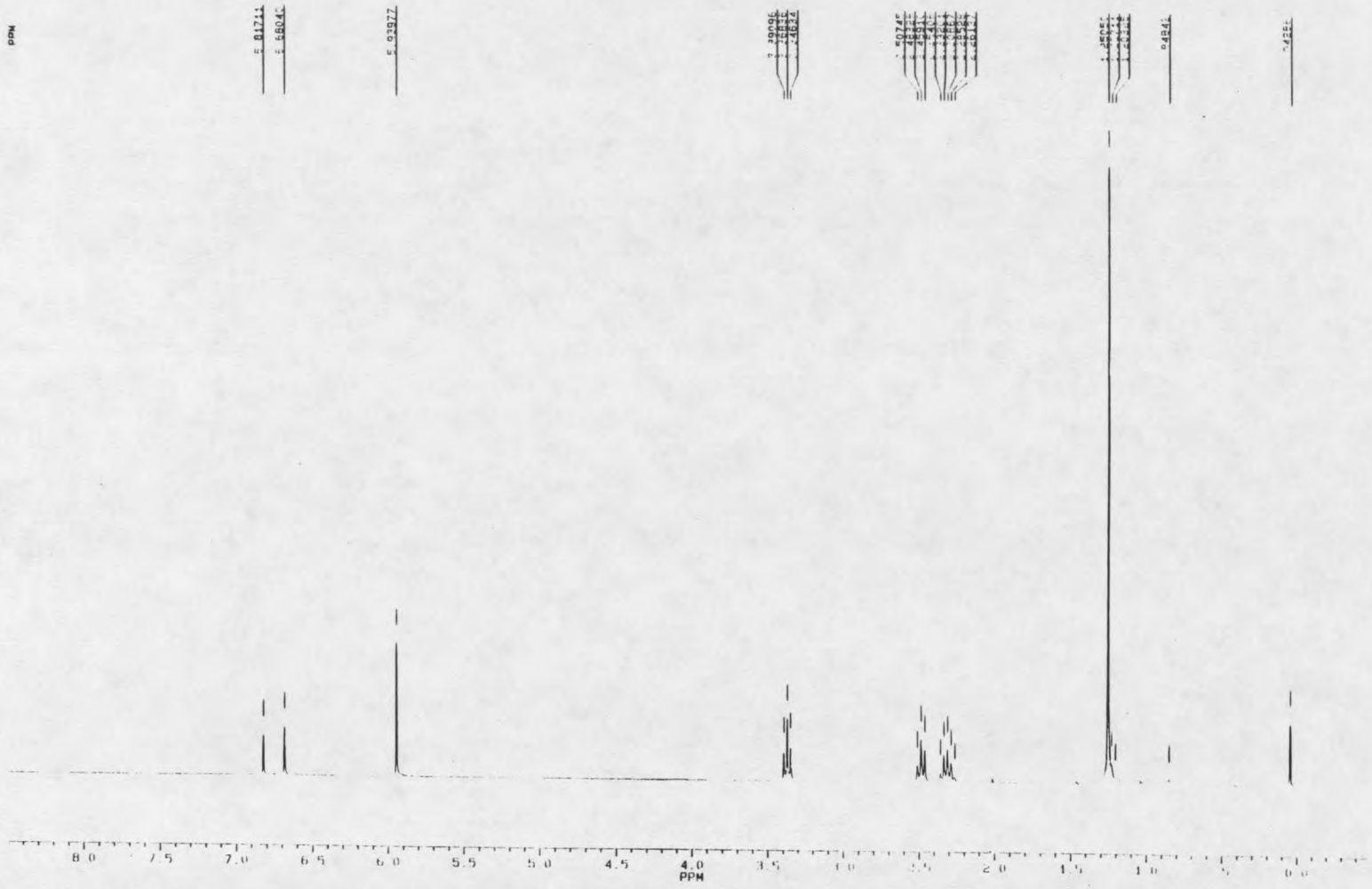


Figure 19. ^{1}H NMR Spectrum of 1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (**25d**).

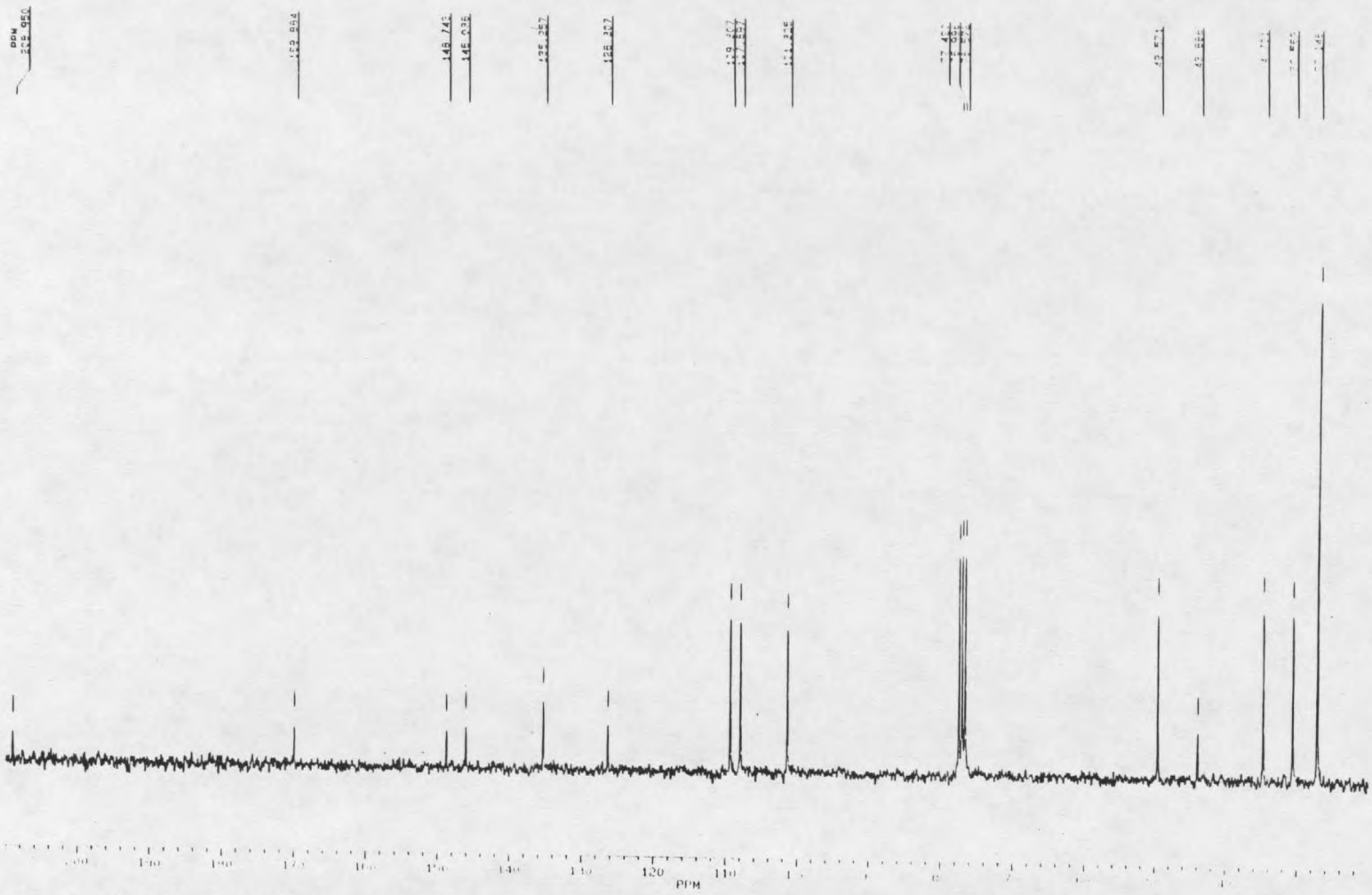


Figure 20. ^{13}C NMR Spectrum of 1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (**25d**).

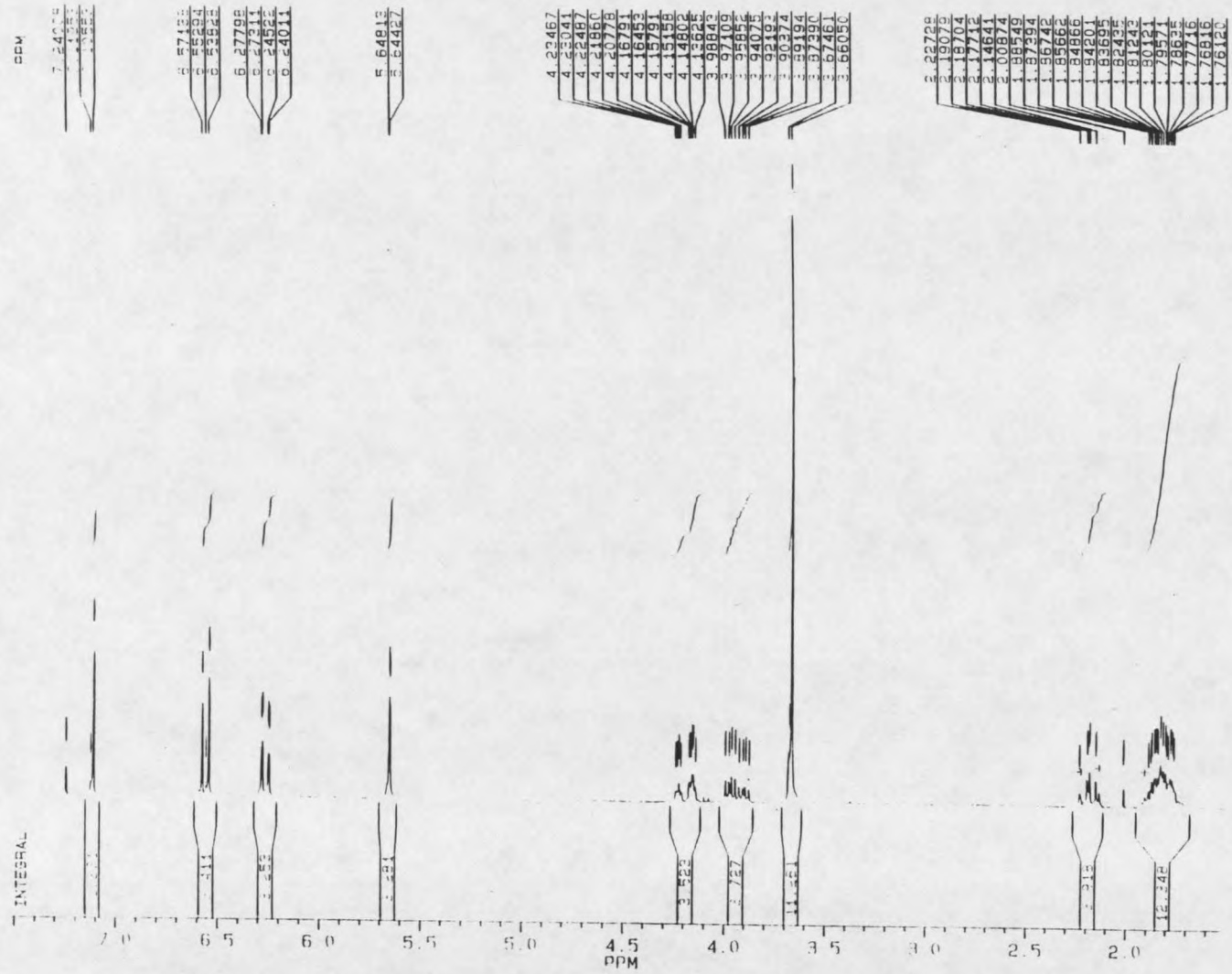


Figure 21. ^{1}H NMR Spectrum of 1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**27**).

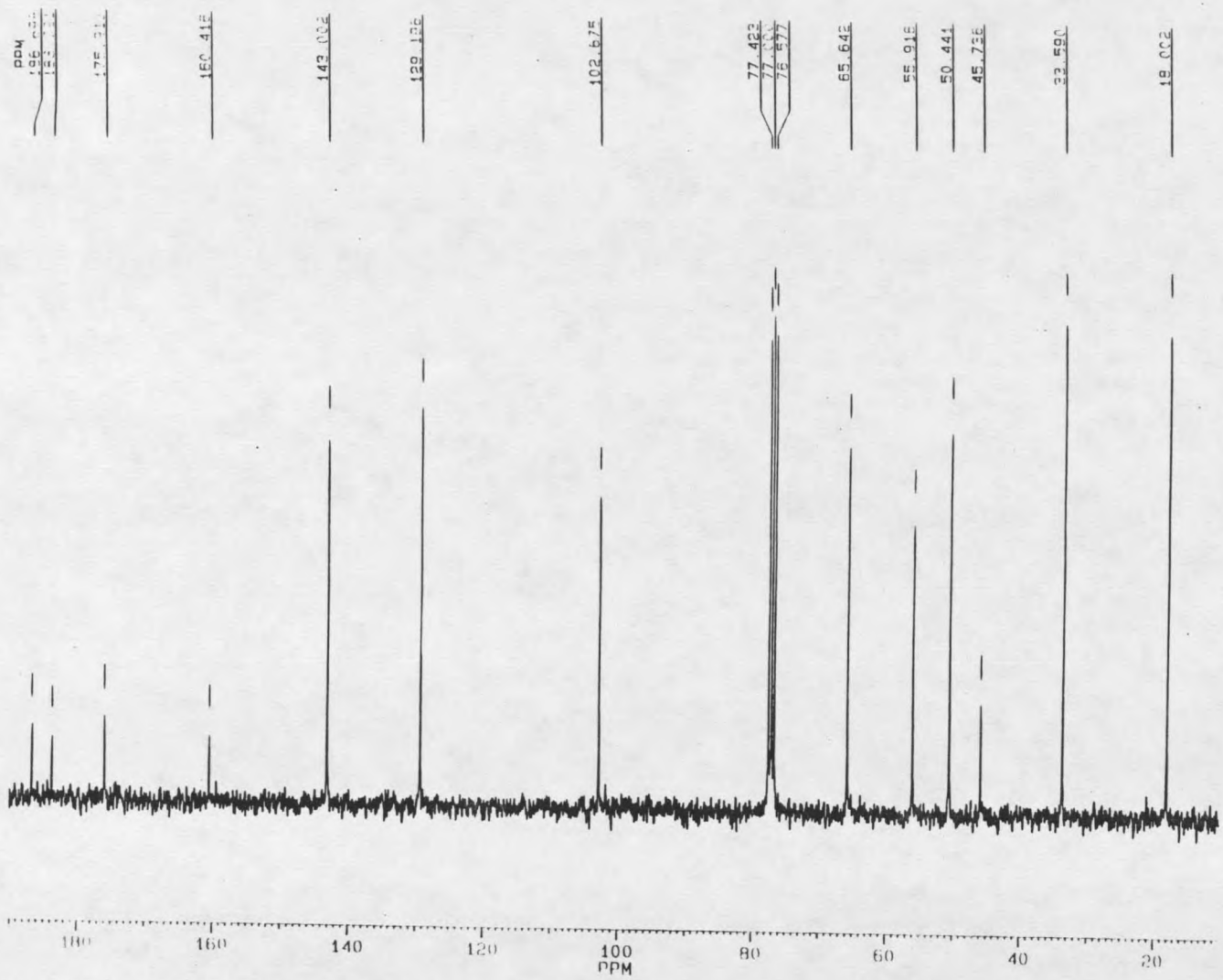


Figure 22. ^{13}C NMR Spectrum of 1-Methoxy-7-dichloroacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**27**).

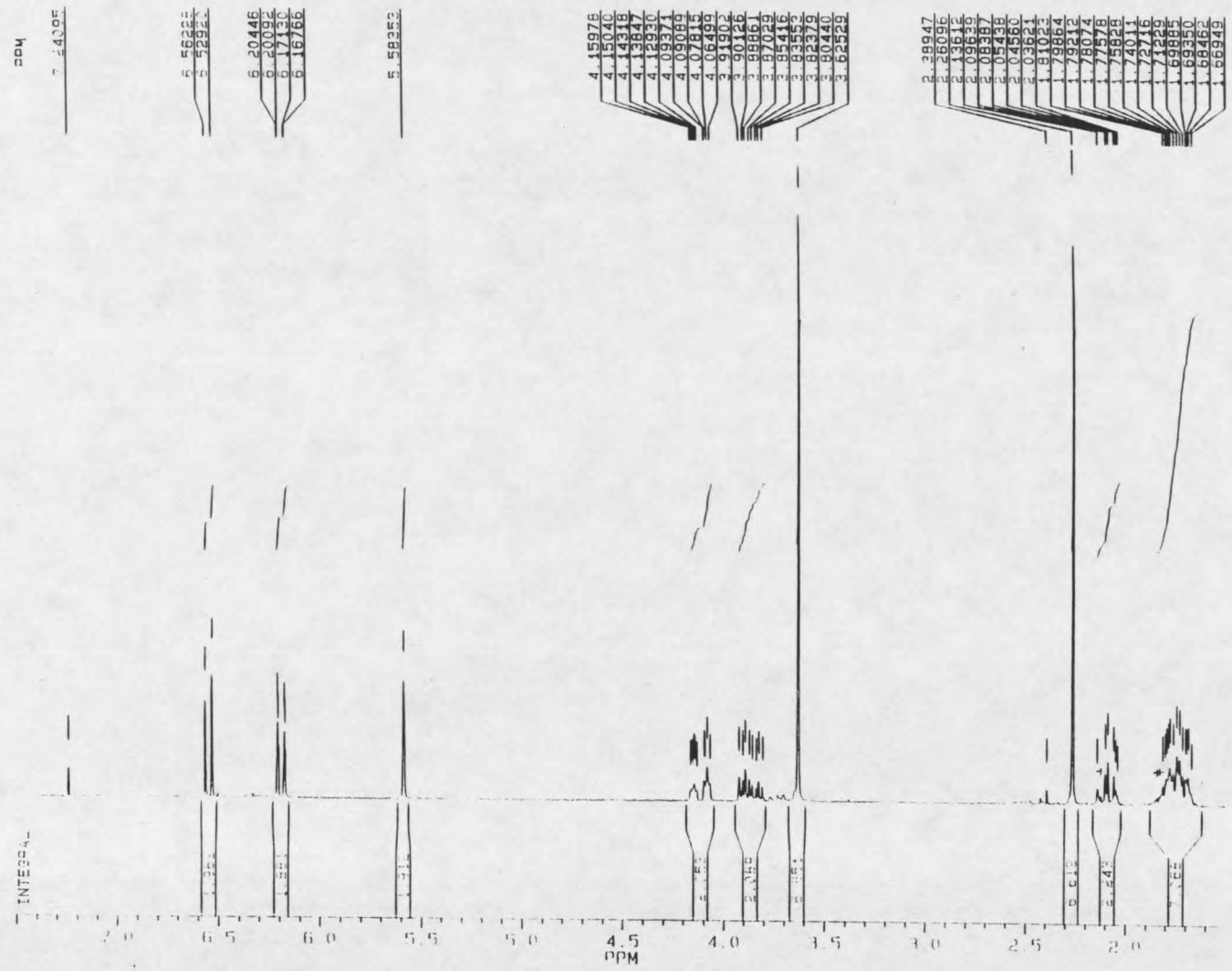


Figure 23. ^{1}H NMR Spectrum of 1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (**38**).

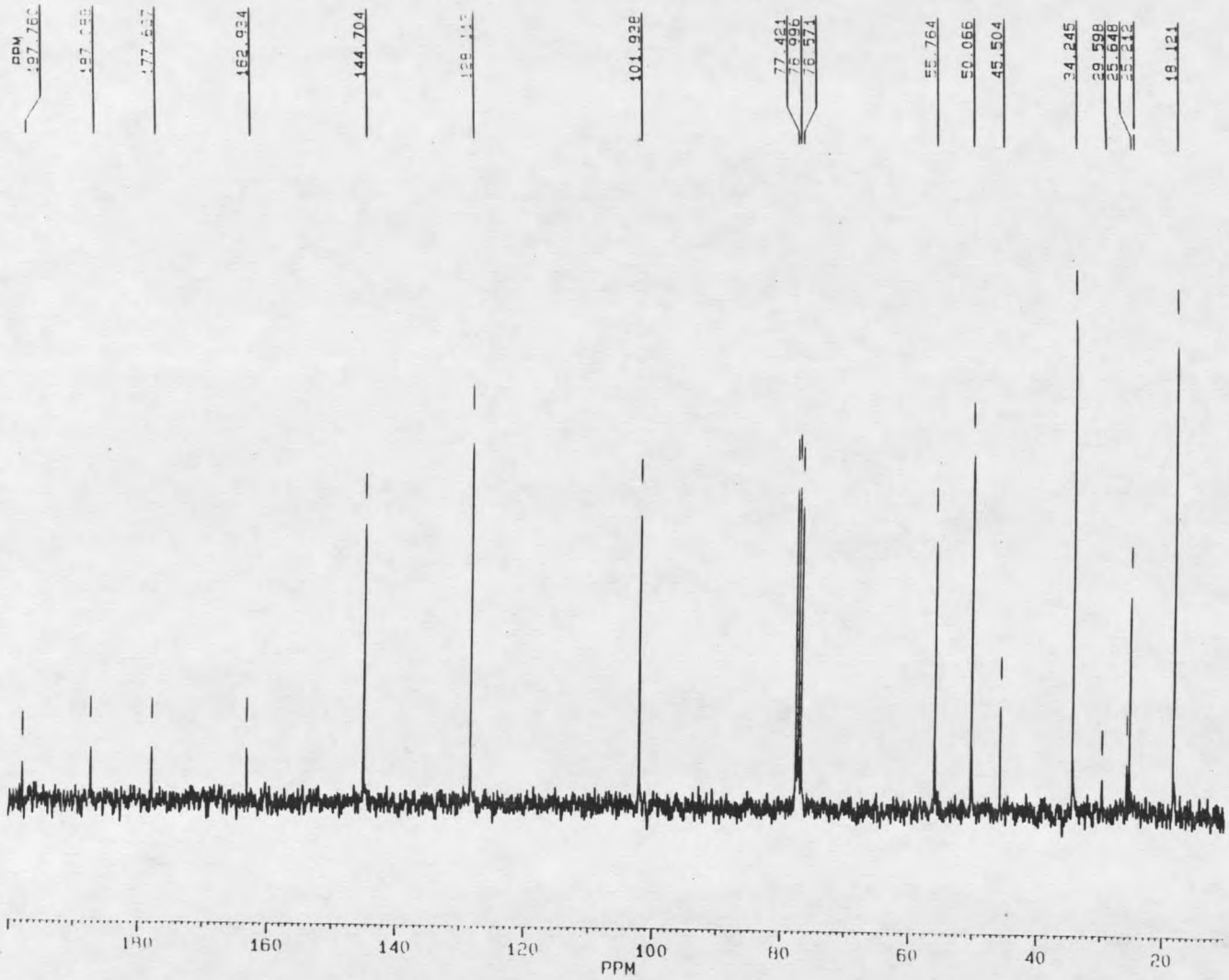


Figure 24. ^{13}C NMR Spectrum of 1-Methoxy-7-acetyl-8-azaspiroundeca-1,4,7-trien-3-one (**38**).

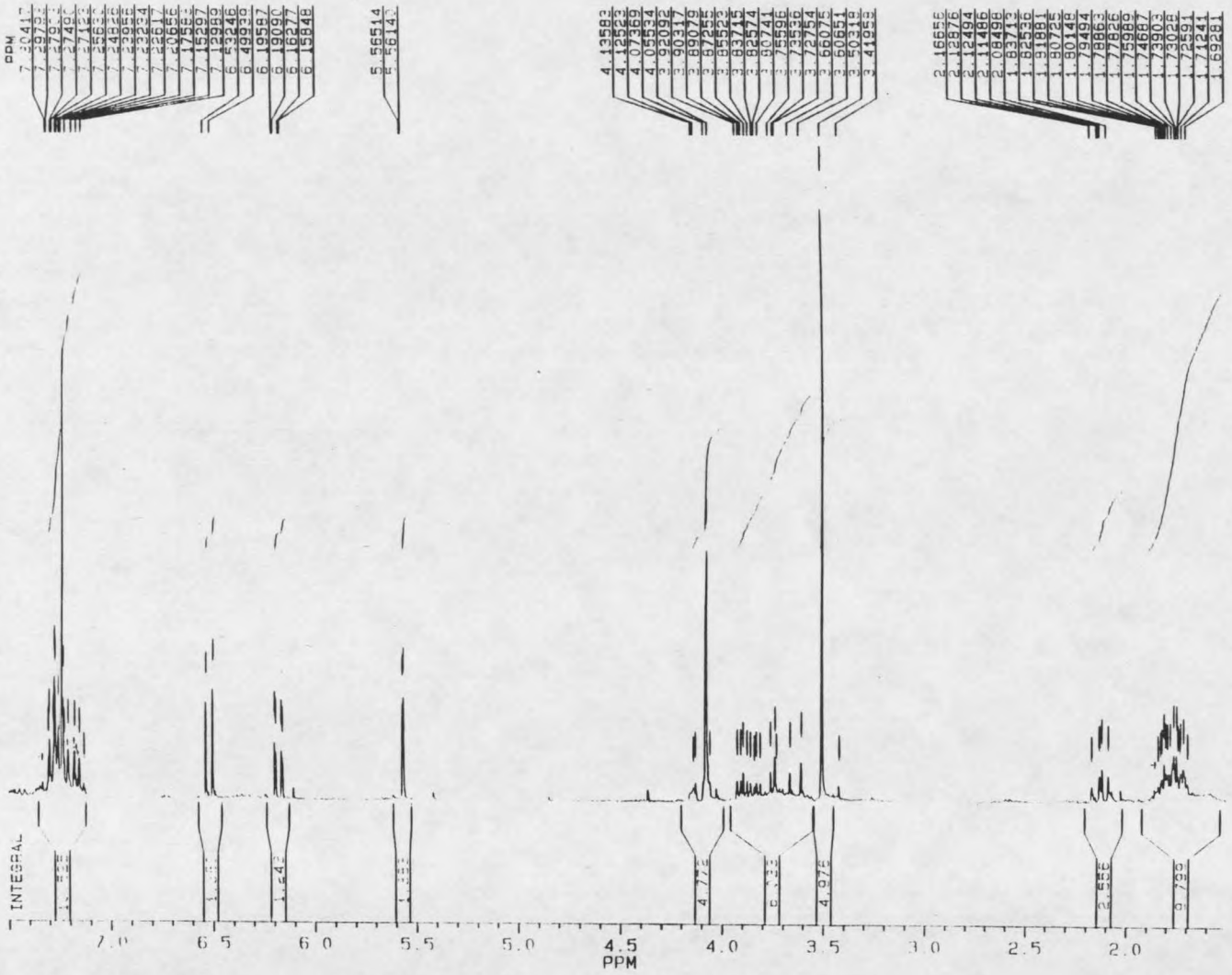


Figure 25. ^{1}H NMR Spectrum of 1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**42**).

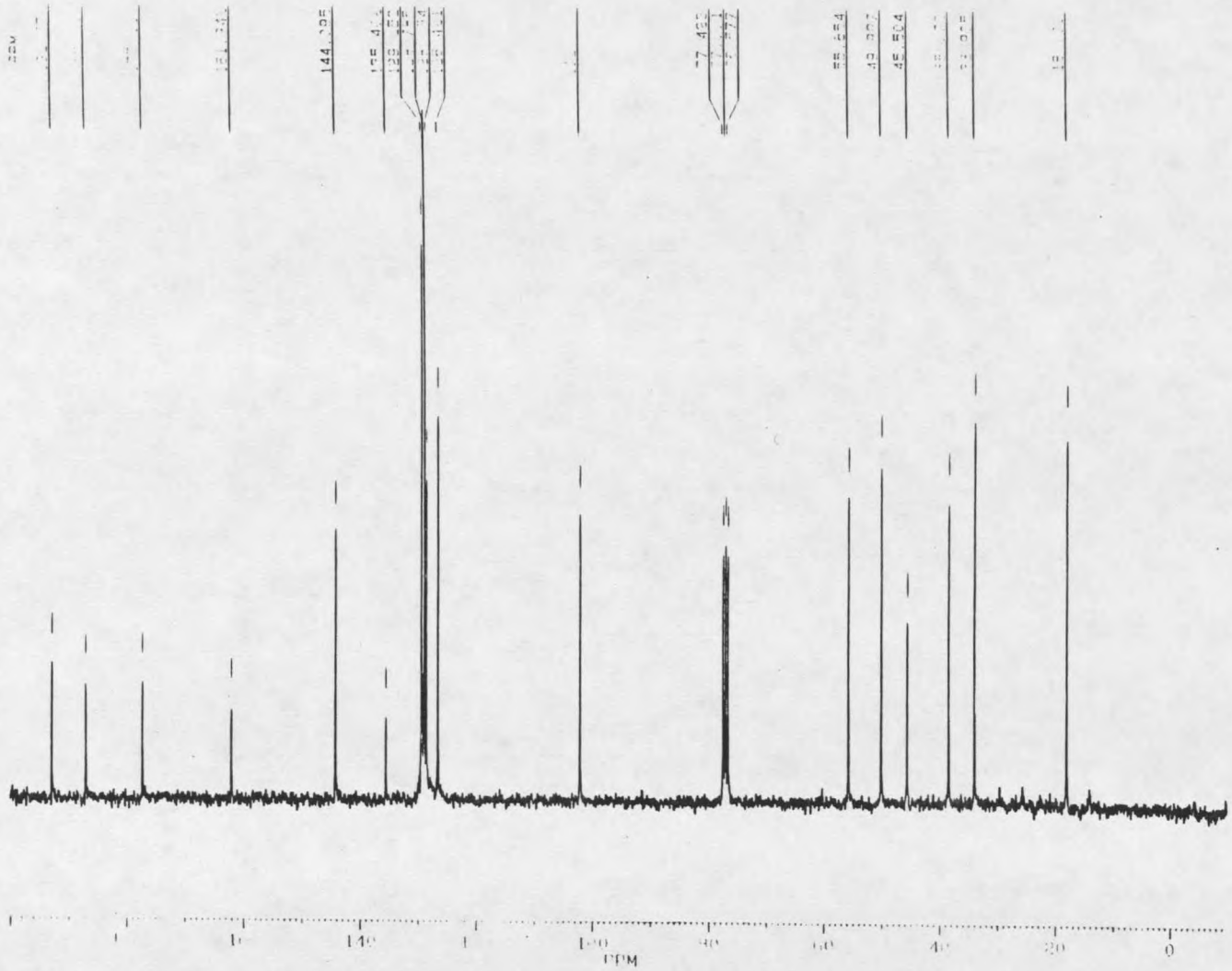


Figure 26. ^{13}C NMR Spectrum of 1-Methoxy-7-phenylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**42**).

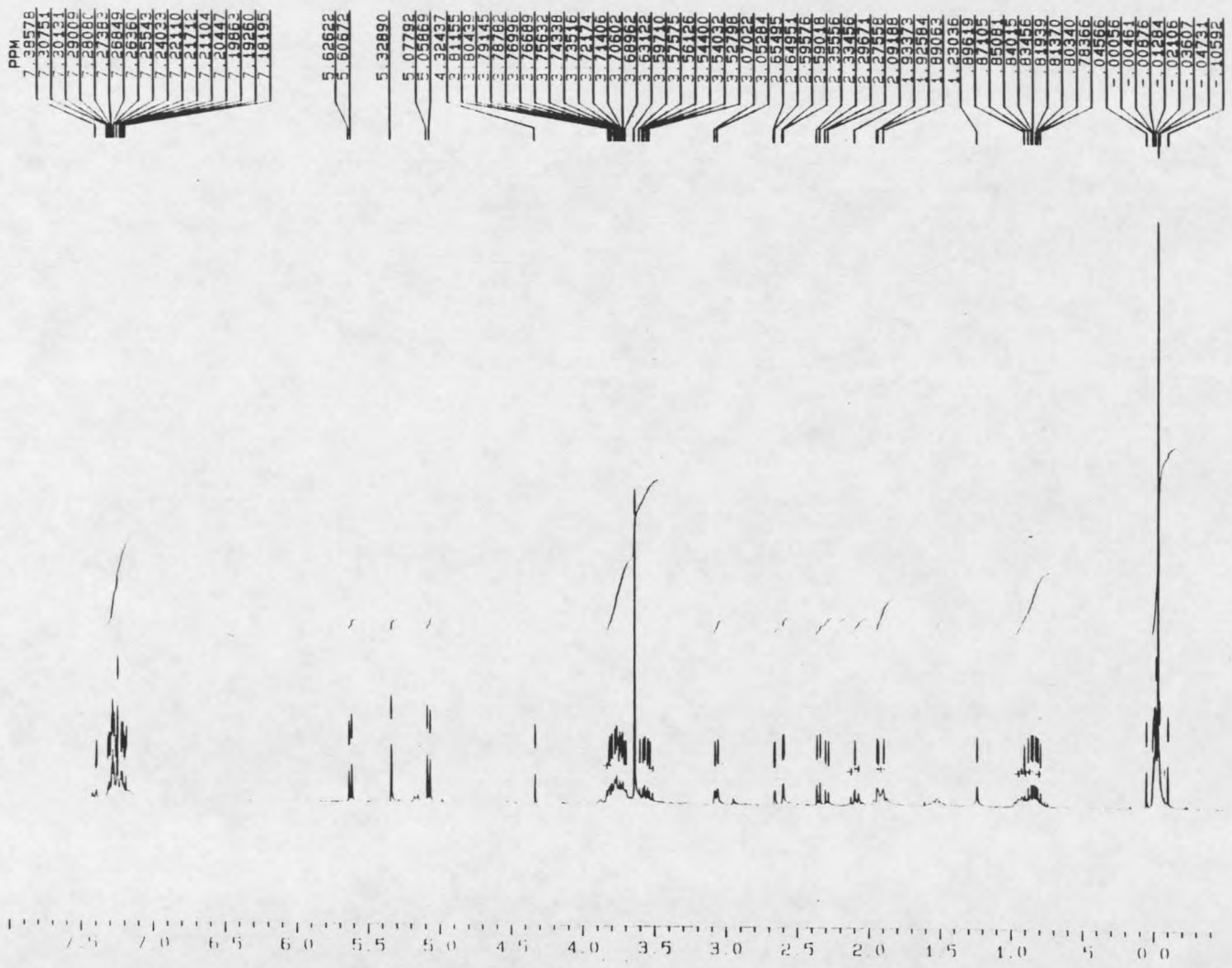


Figure 27. ^{1}H NMR Spectrum of Phenylthio tricyle (**43**).

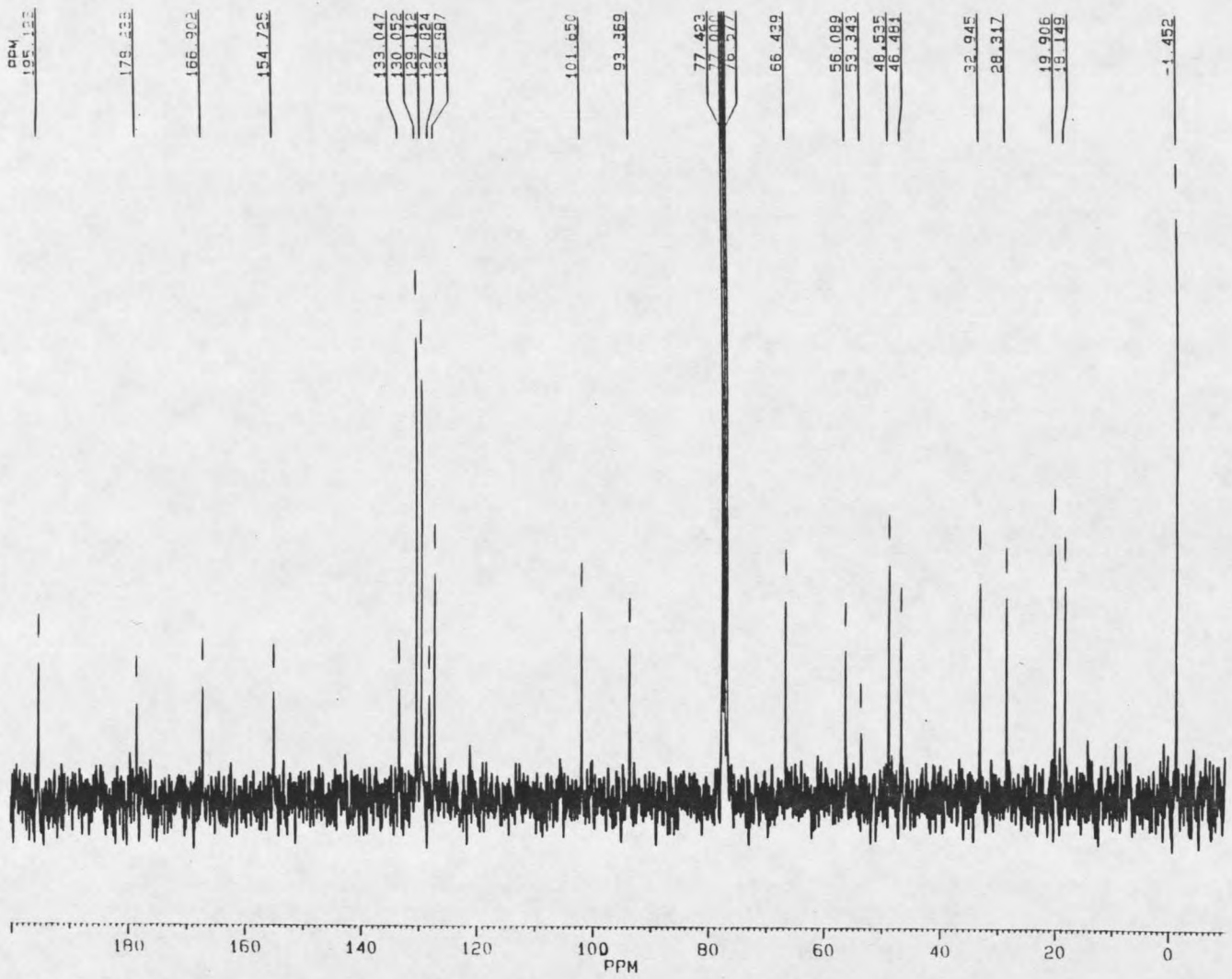


Figure 28. ^{13}C NMR Spectrum of Phenylthio tricyle (**43**).

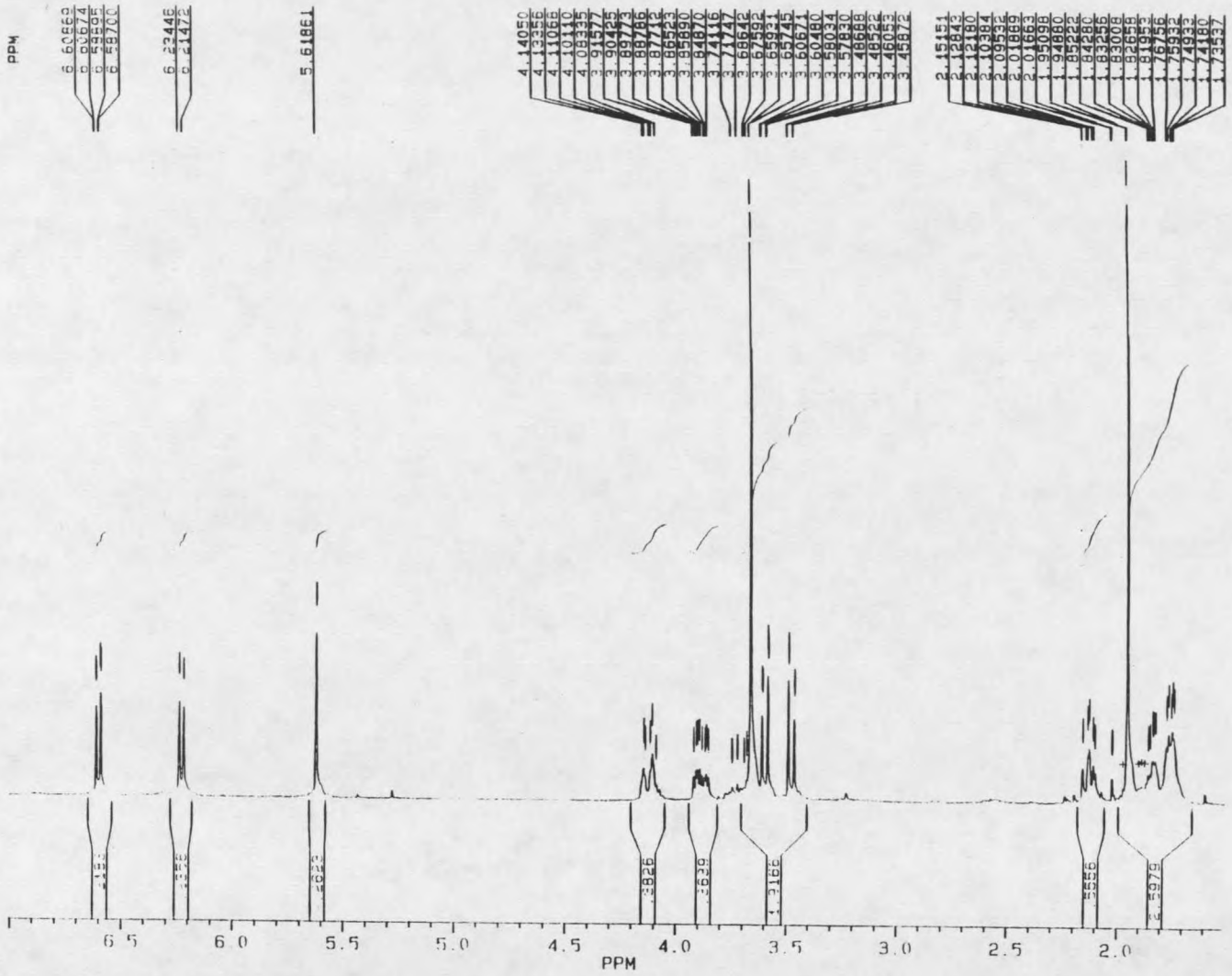


Figure 29. ^{1}H NMR Spectrum of 1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**51**).

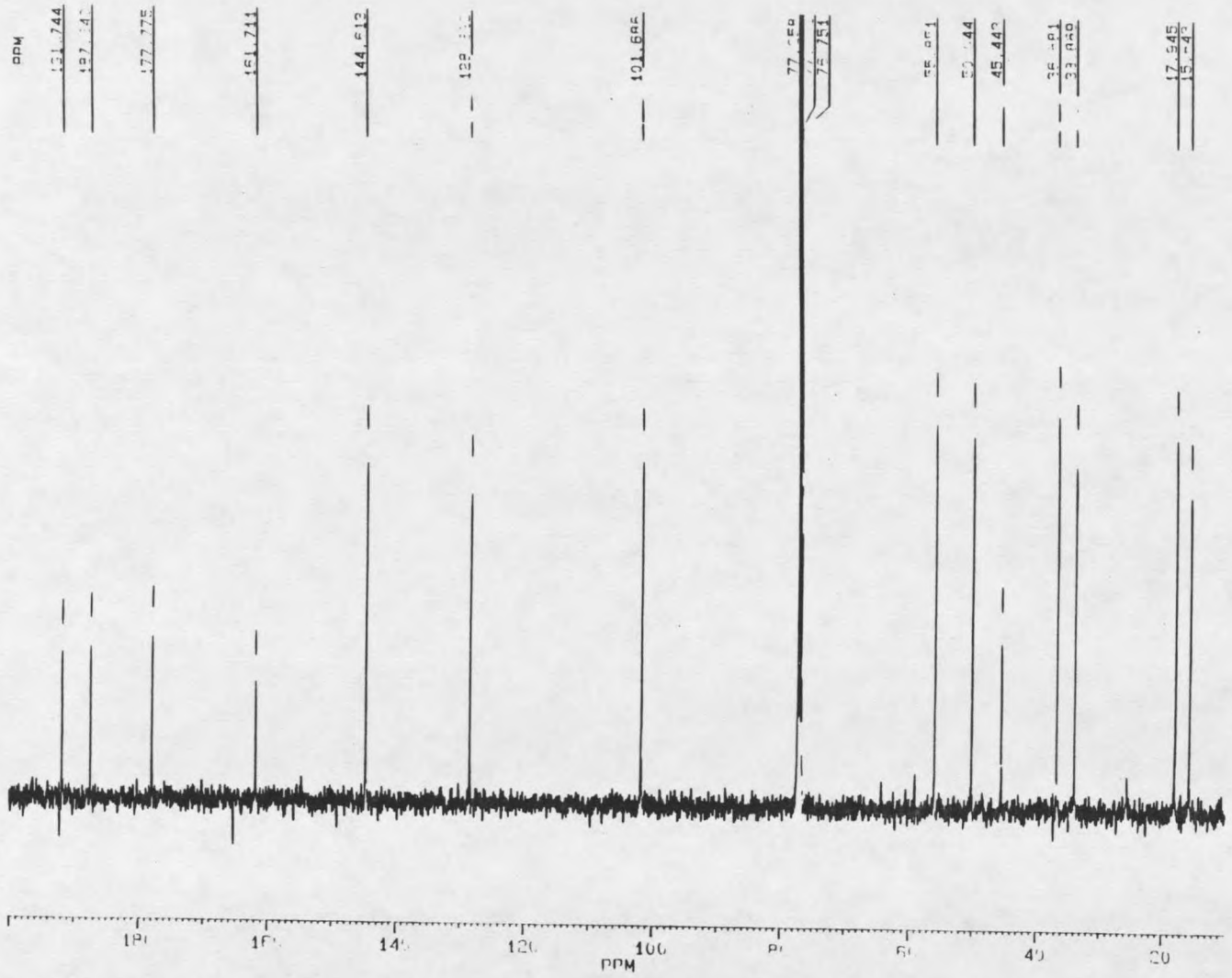


Figure 30. ^{13}C NMR Spectrum of 1-Methoxy-7-methylthioacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**51**).

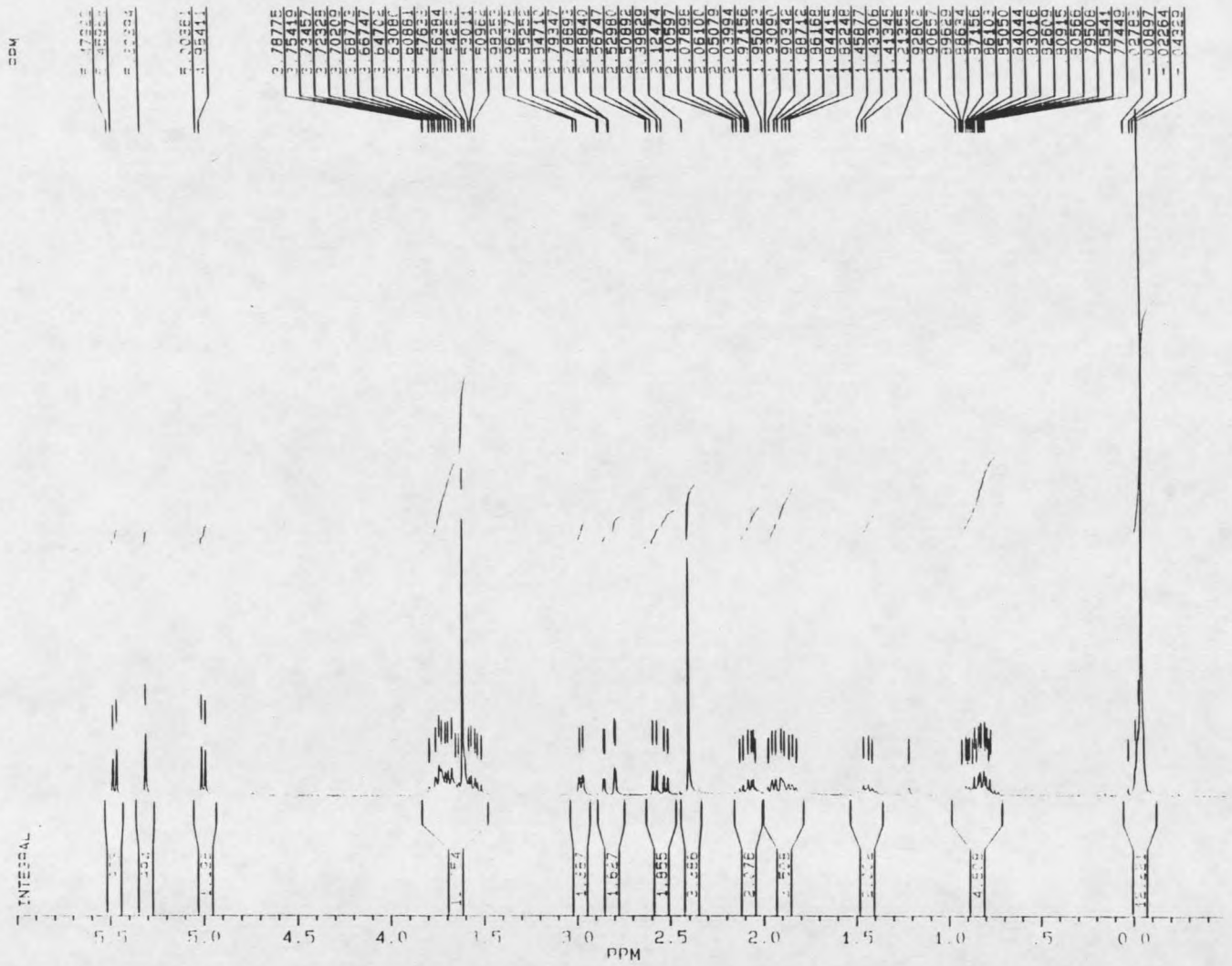


Figure 31. ^{1}H NMR Spectrum of Methylthio tricyle (**52**).

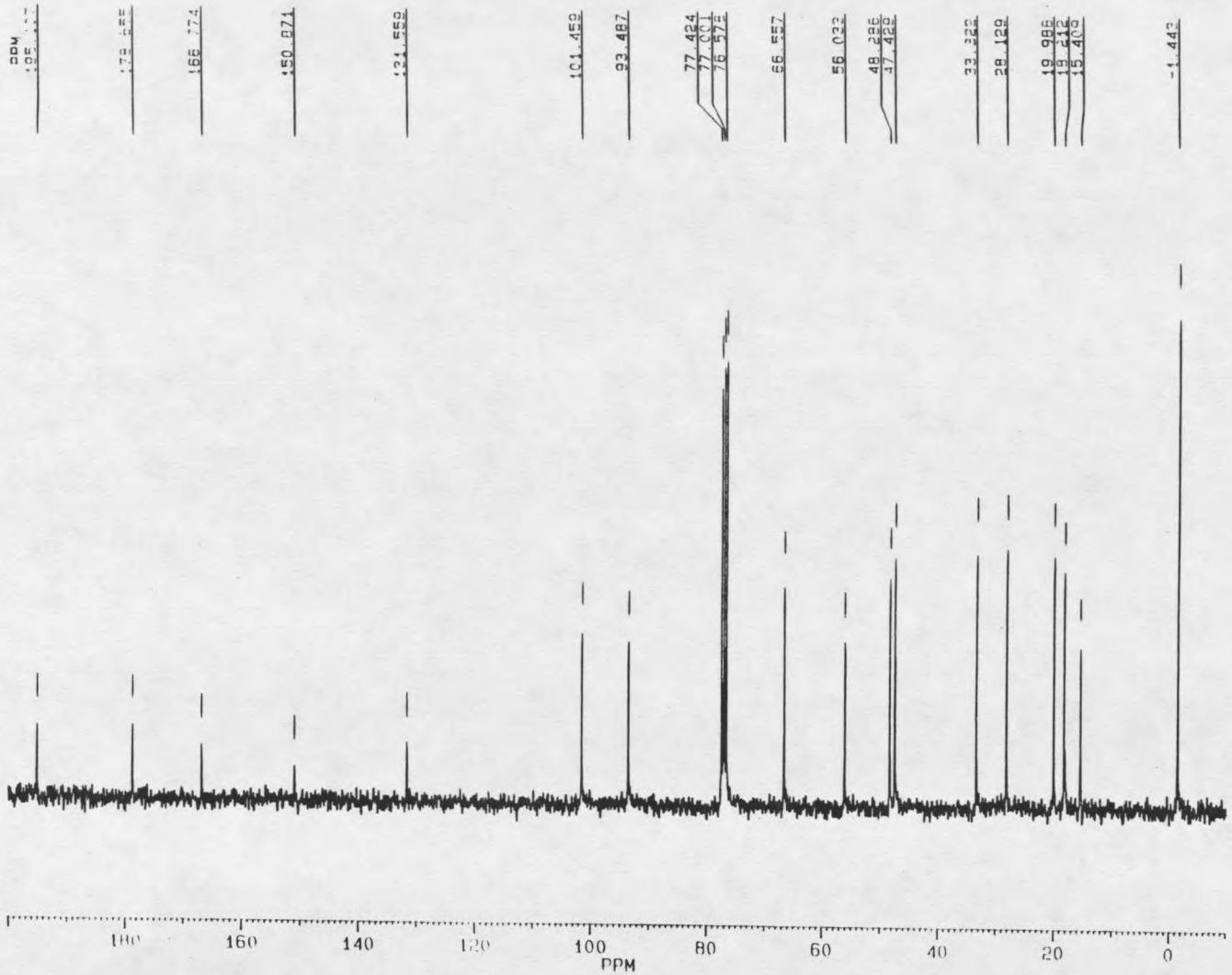


Figure 32. ^{13}C NMR Spectrum of Methylthio tricyle (**52**).

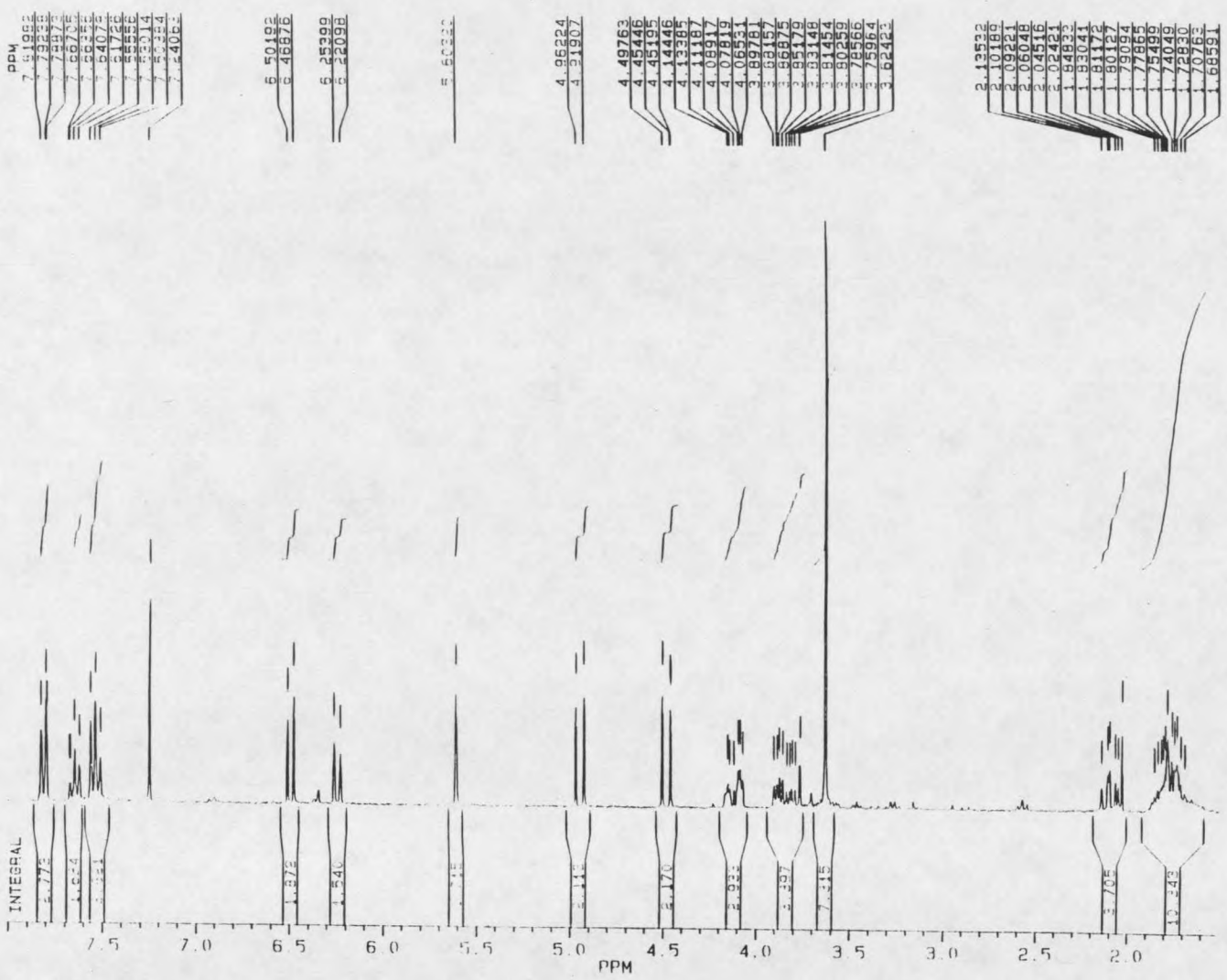


Figure 33. ^{1}H NMR Spectrum of 1-Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**40**).

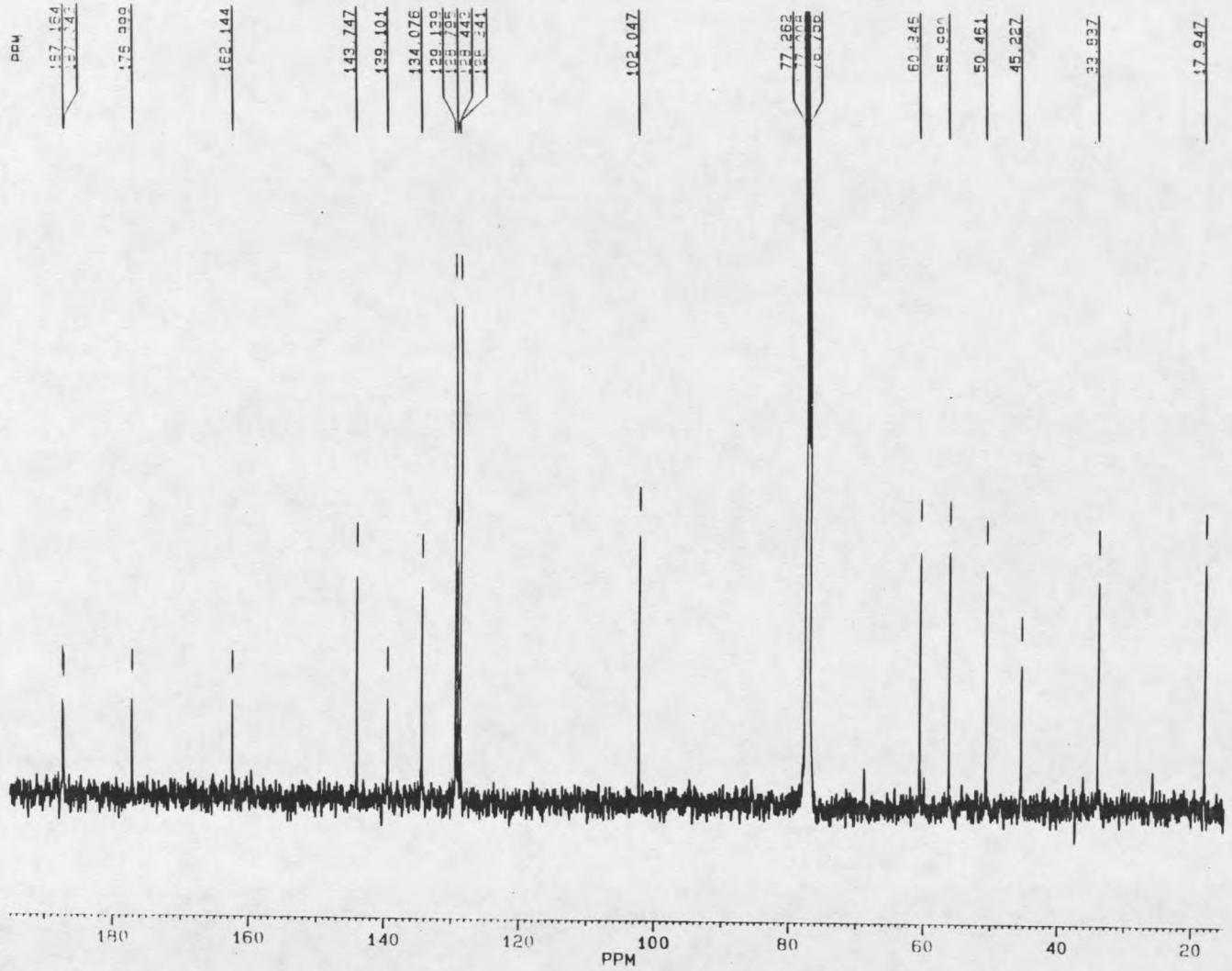


Figure 34. ^{13}C NMR Spectrum of 1-Methoxy-7-phenylsulphonylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (**40**).

MONTANA STATE UNIVERSITY LIBRARIES
3 1762 10255461 3

HOUCHEN
BINDERY LTD
UTICA/OMAHA
NE