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LOYOLA UNIVERSITY OF CHICAGO

# I. A FACILE ROUTE TO ALLYLIC PHOSPHONATES VIA BASE-CATALYZED ISOMERIZATION OF THE CORRESPONDING VINYL PHOSPHONATES

# II. REMOTE DIANIONS IN SYNTHESIS: SYNTHETIC APPROACHES TO THE INDOLIZIDINES

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

BY

JAMES J. KIDDLE

JANUARY 1994

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# ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Dr. James H. Babler for his support, and contribution to Part I of this thesis and to his graduate career. The author also wishes to express his thanks and gratitude to Dr. Charles M. Thompson for his guidance, enthusiasm, friendship, and the opportunity to do research in his laboratory. Thanks are expressed to the members of the dissertation committee: Dr. David S. Crumrine, and Dr. Kenneth W. Olsen for taking time to serve in this capacity and for many helpful discussions. A special thanks is expressed to Dr. Robert M. Moriarty for serving as the outside committee member, and as advisor at University of Illinois at Chicago.

The author would like to thank Dr. Ronald J. Baumgarten, Anne Erskin, Stuart, Harry, Paula, Egle, Bob, and Steve from the Chemistry Department at University of Illinois at Chicago, for their friendship, guidance, and support while in the graduate program at University of Illinois at Chicago.

The author would like to thank his friends, graduate students of the Chemistry Department, especially those of the Thompson group (past and present) who made life and work enjoyable. A special thanks is extended to Dr. John A. Jackson for the knowledge I gained from him.

The author also wishes to thank his parents for their love, support, and

encouragement in everything I have done. Also, to my brothers and sister for their love support, and never letting me lose my sense of humor.

The author wishes to express his deepest thanks to Cindy for her love, patience, understanding, and inspiration which made completing this work and my life easier.

Finally, thanks to all for the "Souvenirs" (especially Jimmy), if we all weren't crazy we would go insane. Also, take care to look for sharks.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AIBN | azo-bis-isobutyronitrile |
| anal | analysis |
| Bn | benzyl |
| n-Bu | n-butyl |
| n-BuLi | n-butyllithium |
| calcd | calculated |
| °C | degrees Celsius |
| cm | centimeter(s) |
| δ | chemical shift in parts per million |
| m-CPBA | meta-Chloroperbenzoic acid |
| cod | cyclooctadienyl |
| DIBAL-H | diisobutylaluminum hydride |
| DMS | dimethyl sulfate |
| DMSO | dimethyl sulfoxide |
| d | doublet |
| dt | doublet of triplets |
| *E* | entgegen (*trans*) |
| equiv | equivalent |
| Et | Ethyl |
| FT | Fourier transform |
| GC | gas chromatography |
| g | gram(s) |
| Hz | hertz |
| HWE | Horner-Wadsworth-Emmons reaction |
| h | hour(s) |
| HIV | human immunodeficiency virus |
| IR | infrared |
| J | coupling constant (NMR) in hertz |

| | |
|---|---|
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| Me | methyl |
| mg | milligram(s) |
| mL | milliliter(s) |
| m | multiplet |
| M | moles per liter |
| m/z | mass to charge ratio (in mass spectroscopy) |
| MHz | megahertz |
| min | minute(s) |
| mmol | millimole(s) |
| mp | melting point |
| Ms | methanesulfonyl (mesyl) |
| NMR | nuclear magnetic resonance |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| Pr | propyl |
| Ph | phenyl |
| ppm | parts per million |
| 4-PSBA | 4-(phenylsulfonyl)butanoic acid |
| q | quartet |
| $R_f$ | retention factor |
| s | singlet |
| t | triplet |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| $Tf_2O$ | trifluoromethanesulfonic anhydride |
| TiPS-$Tf_2O$ | triisopropylsilyl trifluoromethanesulfonate |
| TMS-I | trimethylsilyl iodide |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| Ts | para-toluenesulfonyl (tosyl) |
| *Z* | zusammen (*cis*) |

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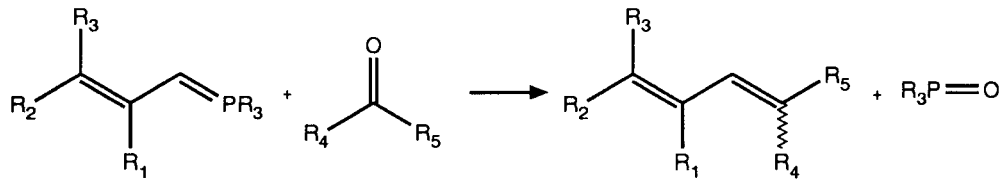
Chapter 1

# INTRODUCTION

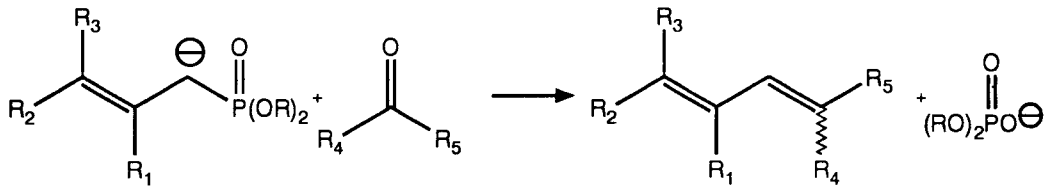
Allylic phosphorus reagents are extremely useful intermediates for the synthesis of conjugated dienes and polyenes. Ylides derived from allylic phosphonium salts have been utilized in industry extensively for the synthesis of retinoids and carotenoids.[1] On the other hand, in spite of their potential utility, allylic phosphonates have seen very little use as reagents for the synthesis of conjugated dienes[2,3] and polyenes.[4-8]

The Wittig reaction[9] of ylides derived from allylic phosphonium salts (**1**)[10] with an aldehyde or ketone (**2**), gives a conjugated diene, (**3**) also a trisubstituted phosphine oxide (**4**), which is usually difficult to separate from the desired olefin (below).




1 2 3 4

In contrast, the Horner-Wadsworth-Emmons reaction (HWE)[11] of an allylic phosphonate[12] (**5**) with an aldehyde or ketone (**2**) produces an identical conjugated diene (**3**) accompanied by a water soluble phosphate anion (**7**) that is easily separated from the reaction mixture (next page).



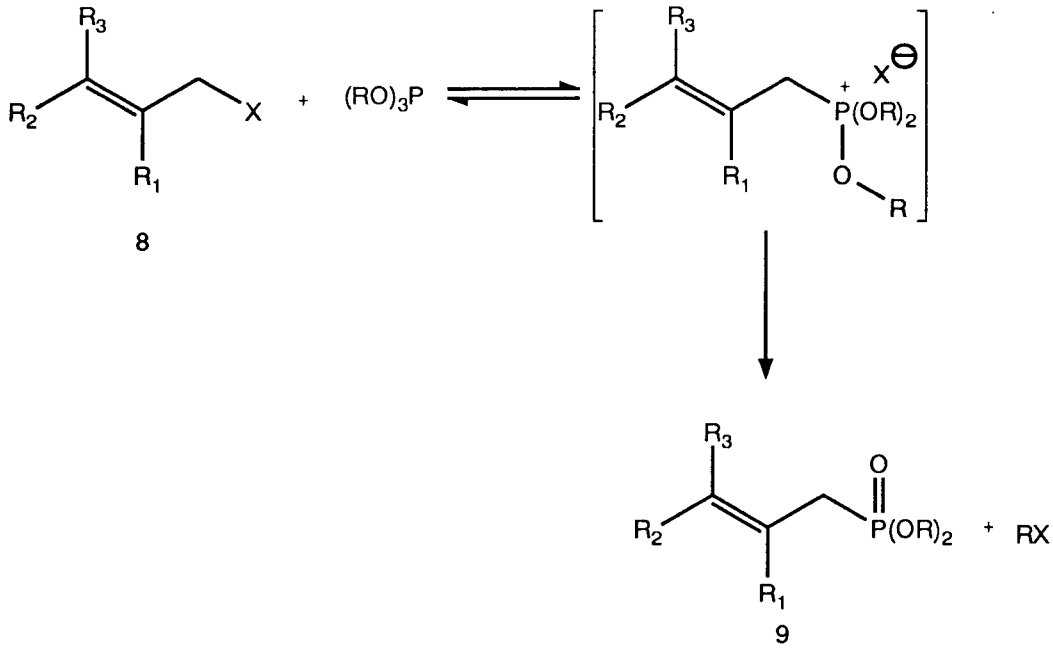
5 2 3 7

In addition to the ease of isolation of products from the HWE reaction, greater control of the olefin stereochemistry is observed. The Wittig reaction of an ylide derived from an allylic phosphonium salt and an aldehyde or ketone often produces mixtures of the (*E*)- and (*Z*)-alkenes. Predominance of the (*E*)-alkene can be accomplished via stabilization of the phosphorus ylide, salt-free conditions, or via β-oxo-ylides.[13] In contrast, under the standard conditions of the HWE reaction of phosphonates with aldehydes or ketones, the (*E*)-alkene is usually the major product.

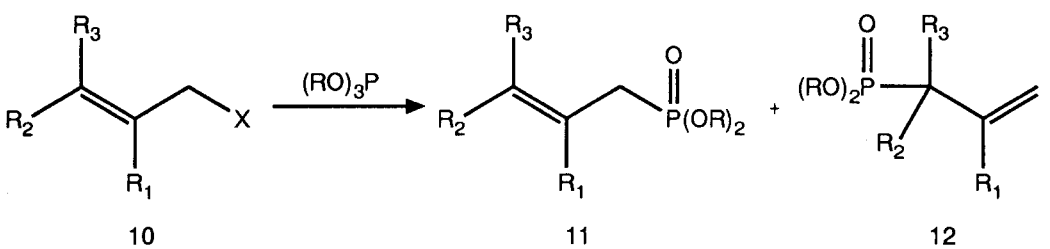
Since allylic phosphonates offer a number of advantages over the corresponding allylic phosphonium ylides, their limited use in synthesis is surprising. There are two reasons that allylic phosphonates have had limited use in synthesis. First, the allylic halide precursors are often unstable under the reaction conditions required for formation of the phosphonates.[14] Second, an electron withdrawing group is often necessary in the α- or γ- position to allow formation of the carbanion under relatively mild conditions.[12] If the electron withdrawing group is not a desired feature of the final product, functional group conversion is required.

The most common approach to the synthesis of allylic phosphonates (**9**) is the Arbuzov reaction, which involves the displacement of a halide from an allylic halide (**8**)

by a trialkyl phosphite.[15]

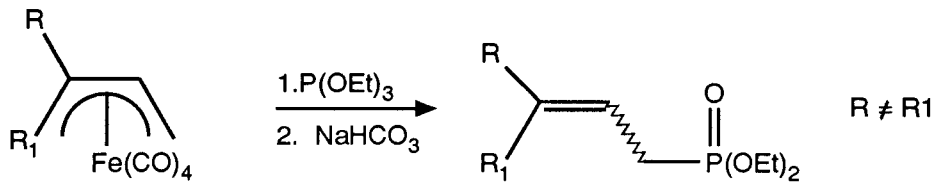



Two features limit the use of the Arbuzov reaction in the formation of HWE precursors. First, substitution in the Arbuzov reaction can take place at either the α- (**11**) or γ-position (**12**) in the allylic halide as is the case when the corresponding allylic phosphonium salts are formed.[16] γ-Substitution in the Arbuzov reaction is especially prevalent with internal allylic halides.[17]



Second, the trialkyl phosphite can function as a Lewis base, thereby causing loss of the stereochemical integrity of the allylic carbon-carbon double bond.

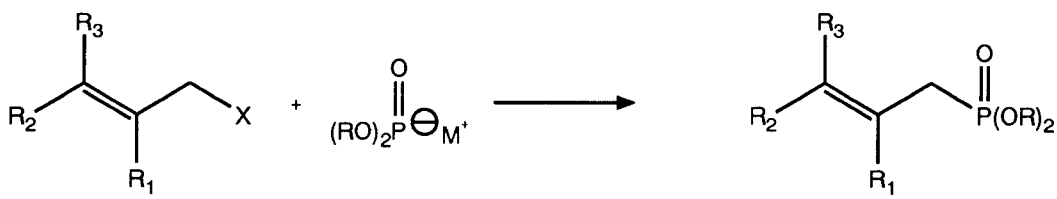
In an effort to circumvent attack at the γ-position, Salzer and co-workers attempted to react conjugated diene-iron carbonyl complexes (**13**) with trialkyl phosphites.[18]




13 14

Although Salzer obtained regioselective attack at the less substituted end of the conjugated diene the reaction was not stereoselective, providing a diastereomeric mixture of allylic phosphonates (**14**).

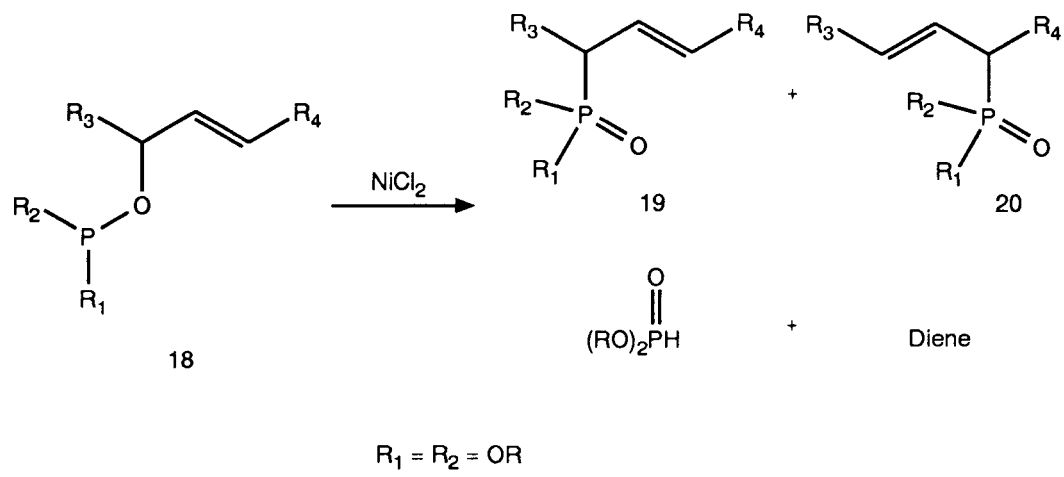
An alternative approach to the Arbuzov synthesis of phosphonates is the Michaelis-Becker reaction, in which an allylic halide (**15**) is reacted with an alkali metal derivative of a dialkyl phosphite (**16**).[19]




15 16 17

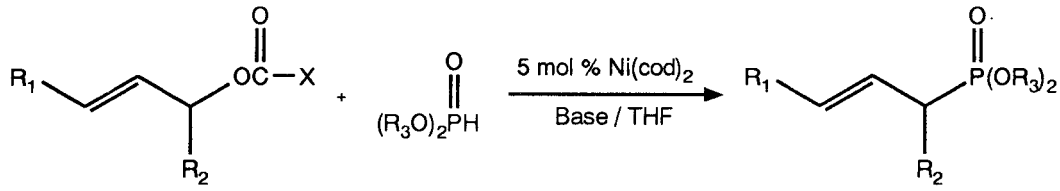
Unfortunately the Michaelis-Becker reaction suffers from the same drawbacks as the Arbuzov reaction namely, γ-position substitution, loss of stereochemical integrity of the allylic double bond, and also elimination reactions.[20]

A number of alternatives to the Arbuzov and Michaelis-Becker reactions have appeared in the literature for the formation of the allylic phosphonates. Zhu and Lu have reacted allylic phosphites (**18**) with $NiCl_2$ to synthesize allylic phosphonates (**19**, **20**)[below].[21]




The rearrangement is not regiospecific providing both α- (**19**) and γ-phosphonates (**20**). In addition, nickel catalyzed rearrangement competes with an elimination reaction to give a dialkyl phosphite and the corresponding diene. In the case of the allylic phosphites derived from 2-cyclohexen-1-ol, 1,3-cyclohexadiene, the elimination product, is formed exclusively with no formation of the corresponding phosphonate. The rearrangement of allylic phosphites has also been attempted using $Ni(cod)_2$[22] providing similar results. In a later paper, Lu and Zhu reacted dialkyl phosphites (**22**) with allyl acetates or carbonates

(**21**) in the presence of $Ni(cod)_2$ in a preparation of allylic phosphonates (**23**).[23]



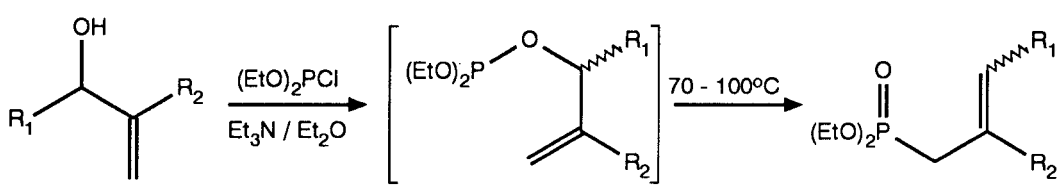

21 22 23

X = R or OR

$R_1$,$R_2$ = alkyl or aryl

Initial attempts using triethylamine as base in the above reaction produced the desired allylic phosphonates in low yield. However, substitution of bis(trimethylsilyl)acetamide (BSA) as base provided the allylic phosphonates in moderate to good yields.

Bodalski and Janecki have synthesized allyl phosphonates by thermally induced Arbuzov rearrangement of preformed trialkyl phosphites.[24]

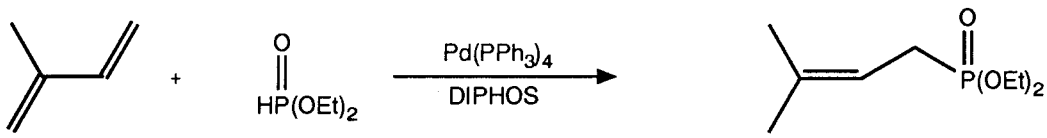



24 25

The trialkyl phosphite is synthesized from the corresponding allylic alcohol (**24**) and diethyl phosphorochloridite to avoid possible competing reactions encountered in the traditional Arbuzov reaction of trialkyl phosphites and alkyl halides. The crude

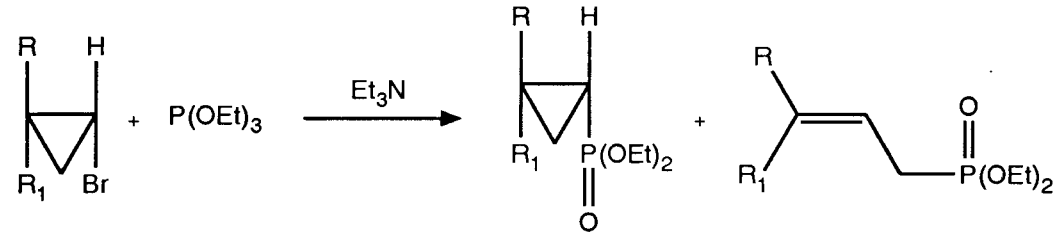
intermediate is heated to induce rearrangement to the desired allylic phosphonate (**25**) in good yield. The stereoselectivity is dependent on the nature of $R_2$. When $R_2 = CO_2CH_3$ the reaction affords exclusively the (*Z*)-olefin whereas when $R_2 = CN$ a mixture of (*E*)- and (*Z*)-olefins is produced.

Hirao and co-workers have utilized a palladium-catalyzed synthesis of phosphonates from alkyl halides and dialkyl phosphites.[25] The reaction of aryl and vinyl halides using this methodology produced the desired phosphonates in moderate to good yields. As an extension, Hirao and co-workers attempted to synthesize an allylic phosphonate (**28**) from a conjugated diene using tetrakis(triphenylphosphine)palladium as a catalyst with 1,2-bis(diphenylphosphino)ethane (DIPHOS) and isoprene (**26**). Unfortunately the reaction proceeded in only 10% yield.




26 27 28

In a later paper Hirao and co-workers, in an attempt to synthesize cyclopropyl phosphonates (**30**) via Arbuzov reaction of substituted cyclopropyl bromides (**29**) and trialkyl phosphites, discovered that the corresponding allylic phosphonate (**31**) had been produced by ring cleavage.[26]

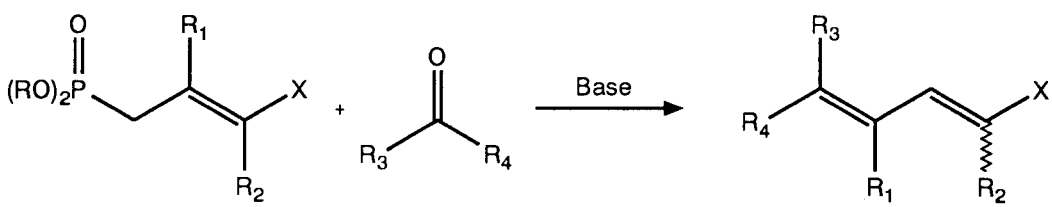



29 30 31

It is interesting to note that regardless of the nature of R and $R_1$ the allylic phosphonate is formed preferentially from 1.5:1 to 14:1 over the desired cyclopropyl phosphonate.

Although the number of methods for the regio- and stereoselective synthesis of allylic phosphonates is rather small, the variety of reactions these reagents can undergo makes them versatile reagents in organic synthesis. Their most important application is the HWE coupling reaction between allylic phosphonates and aldehydes or ketones to provide conjugated dienes in a regio- and stereoselective fashion.

Lavielle and Sturtz[2] used allylic phosphonates (**32**) to synthesize a variety of functionalized 1,3-dienes (**34**) in good yield.

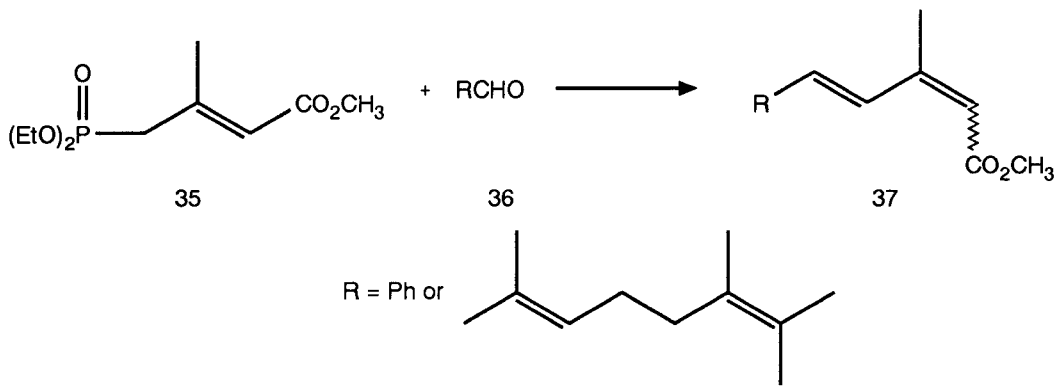



32 33 34

X = OR, SR, $NR_2$

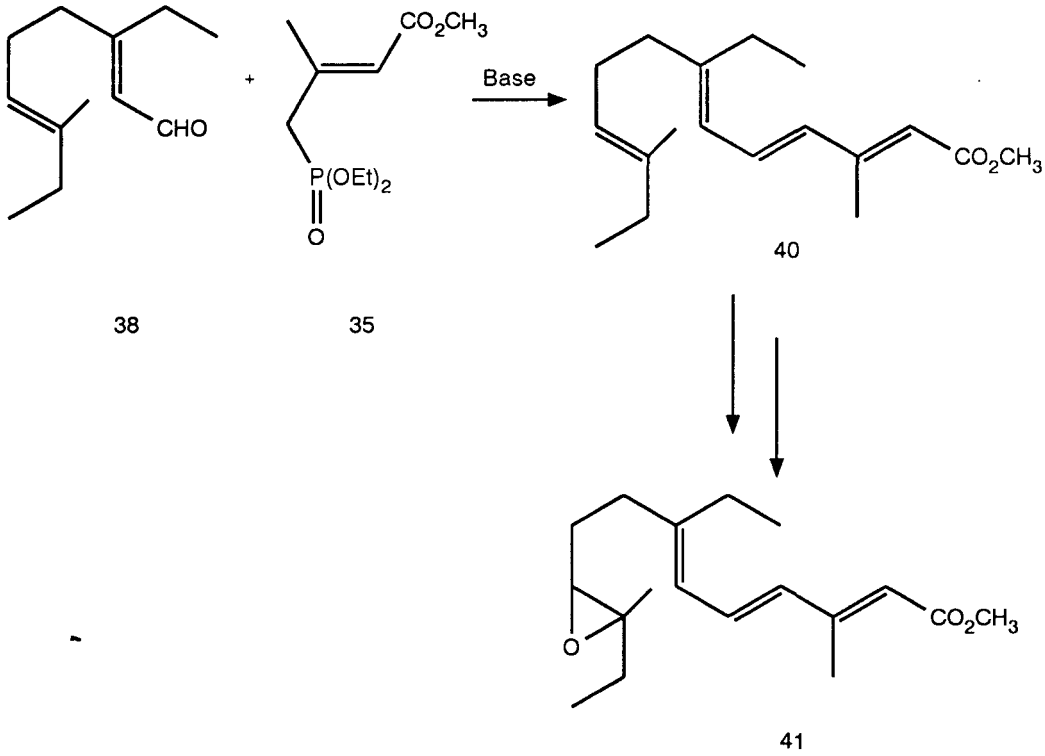
Although no stereochemistry was reported, it is likely that a mixture of (*E*)- and (*Z*)-olefins would be obtained depending on the stereochemistry of the allylic phosphonate.

Pattenden and Weedon[5] have examined the stereochemistry of olefin formation in relation to the geometry of the allylic phosphonate. Reaction of *trans*-4-diethyl



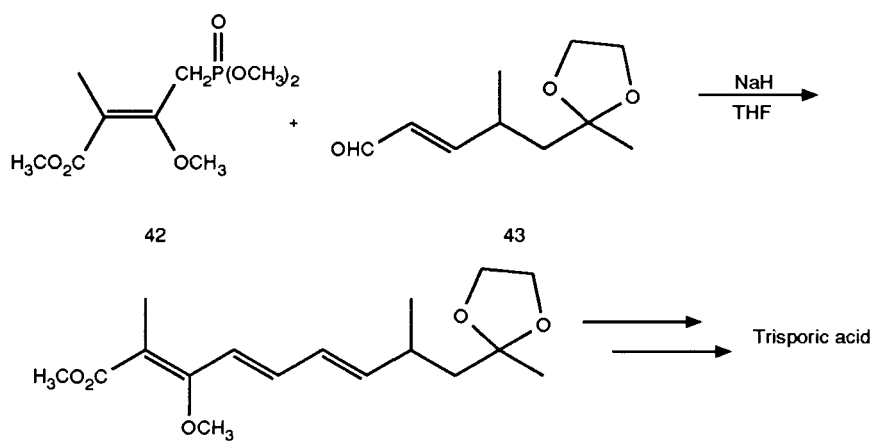

phosphono-3-methyl-2-butenoate (**35**) with either benzaldehyde or (*Z*)-citral (**36**) provides a product in which the stereochemical integrity of the double bond in the allylic phosphonate has been maintained. Reaction of the *cis*-4-diethylphosphono-3-methyl-2-butenoate with either aldehyde gave only 25% of the desired *cis*-ester, the remainder being *trans*-ester (**37**) owing to stereomutation during the reaction.

Allylic phosphonates have also been used extensively in the synthesis of insect biomolecules. Corey and co-workers have synthesized the juvenile hormone from *Hyalophora Cecropia*[27,28] as well as, the dehydro derivative[29] utilizing the allylic phosphonate ester, (**35**) as illistrated in the equation shown below.



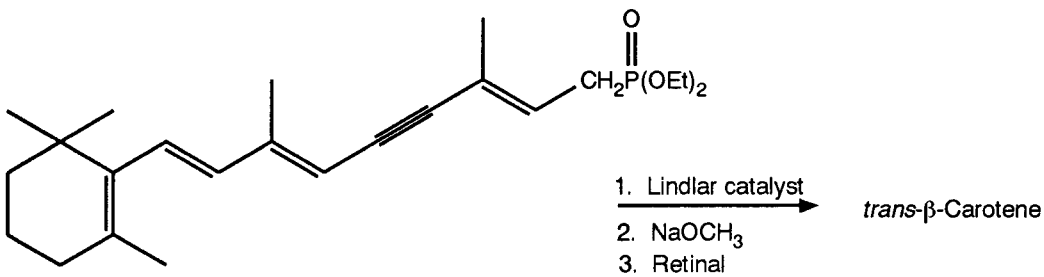

38 35 40 41

Edwards and co-workers have utilized a similar allylic phosphonate ester (**42**) to synthesize the fungal sex hormone trisporic acid.[8] Although the target molecule was isolated as the all *trans* isomer, (**44**) no explanation for the stereocontrol is given.



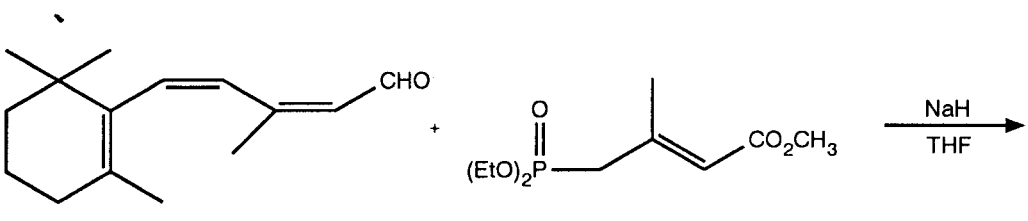

42 43 44

As mentioned previously, allylic phosphonates have seen limited use as carotenoid precursors due to inherent difficulties in formation, although some examples have appeared in the literature. Surmatis and Thommen reacted retinyl allylic phosphonate (**45**) with retinal to provide *trans*-β-carotene in 61% yield based on recovered retinal.[30]

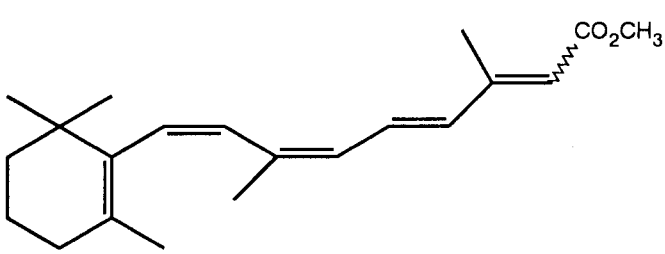



45

Liu and Asato have reacted methyl *trans*-4-diethylphosphono-3-methyl-2-butenoate (**35**) with an aldehyde to provide two isomeric retinoids (**48**).[4]




46 35



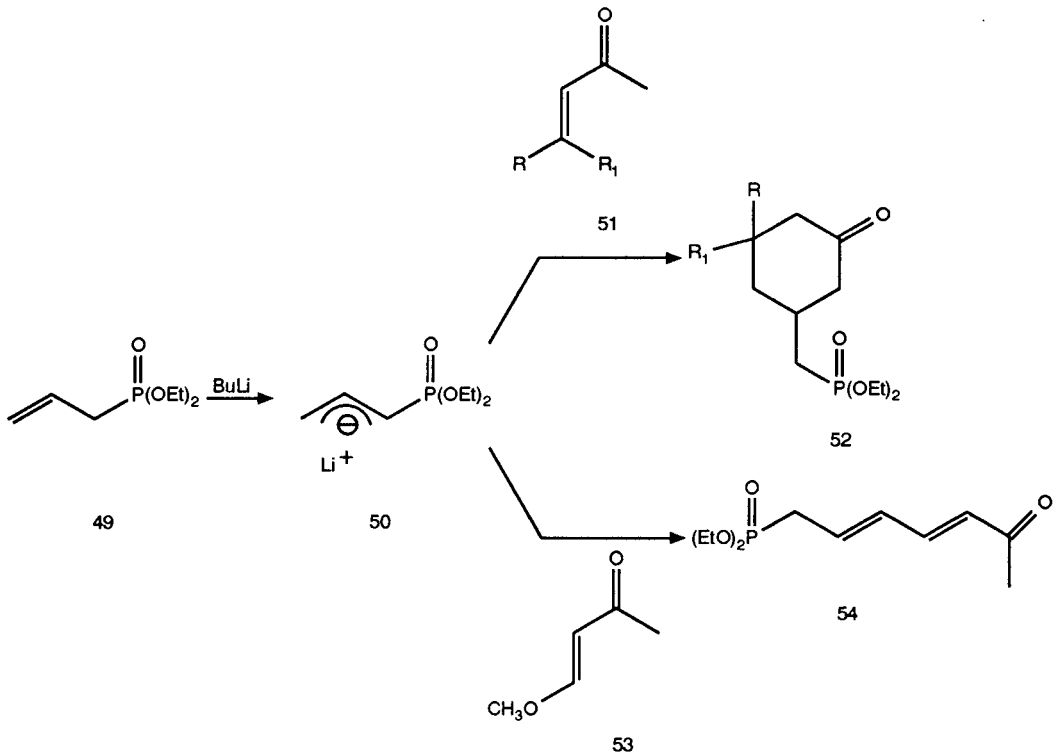

48

The resulting mixture of 7-*cis*, 9-*cis* and 7-*cis*, 9-*cis*, 13-*cis* retinoids is not in accord with earlier reports of Pattenden and Weedon that showed the configuration of the *trans* double bond in the allylic phosphonate to be maintained in the products. The authors did not offer an explanation for this discrepancy.

Allylic phosphonates have also been shown to react with Michael acceptors in conjugate addition reactions. Modro and co-workers[31] have synthesized a variety of acyclic (**54**) and cyclic (**52**) phosphonates via the lithiated salt of diethyl prop-2-enyl phosphonate (**50**) (Scheme I). The reaction provides paths to a number of new intermediates for further HWE reactions.

In conclusion, allylic phosphonates are extremely useful reagents for the synthesis of conjugated dienes and polyenes but have seen limited use due to few reliable methods to provide high yielding and stereoselective syntheses.

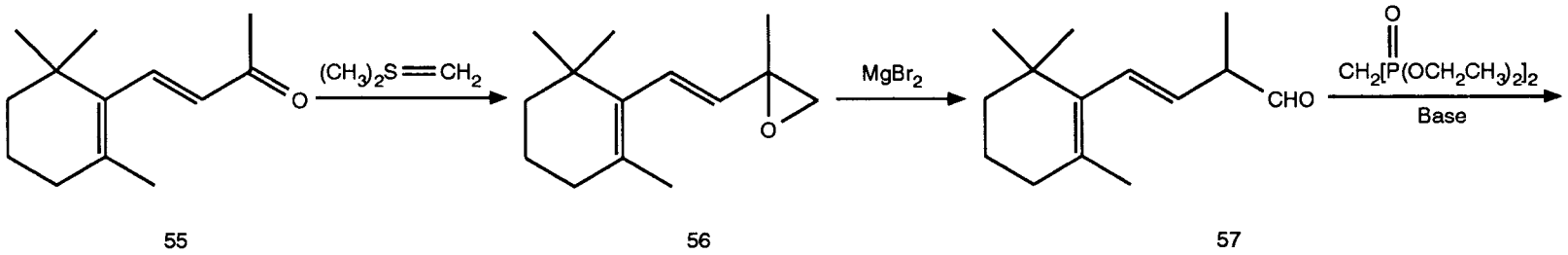
Scheme I. Reaction of the lithiated salt of diethyl prop-2-enyl phosphonate.



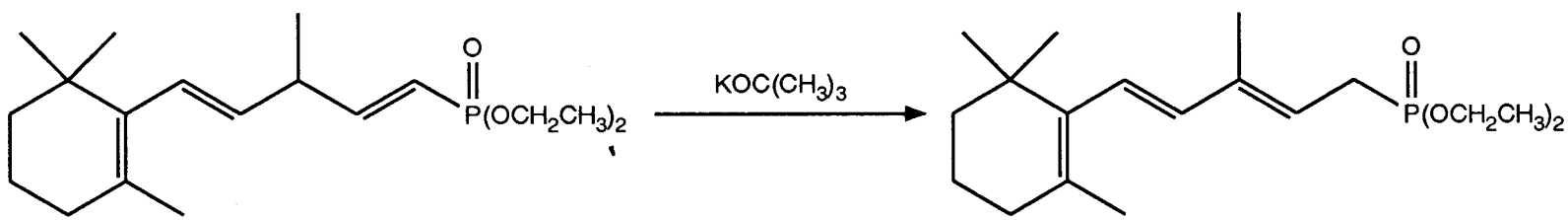
Synthetic Approach - Historical

Recently Babler and Schlidt[32] reported a novel synthesis of all-*trans*-retinoic acid (**60**). The key step of the synthetic approach involves the isomerization of vinyl phosphonate **58** to the corresponding allylic phosphonate **59** (Scheme II). *A priori*, this route did not seem feasible since analogous allylic phosphonium salts are known to isomerize to the corresponding vinyl phosphonium salts in the presence of base [i.e., the reverse of the boxed equation].[33] In addition, the isomerization of allylic phosphonates to vinyl phosphonates has been reported[34] using alkali metal hydroxides. The successful and novel isomerization of **58** to **59** prompted a further study of the scope of this methodology as a possible stereocontrolled approach to allylic phosphonates.

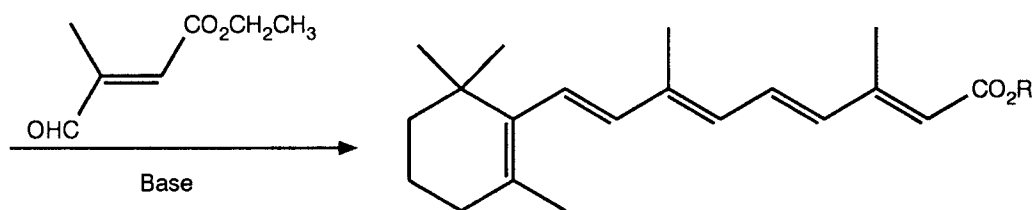
Scheme II. Synthesis of all-*trans*-retinoic acid.




55 56 57




58 59




60

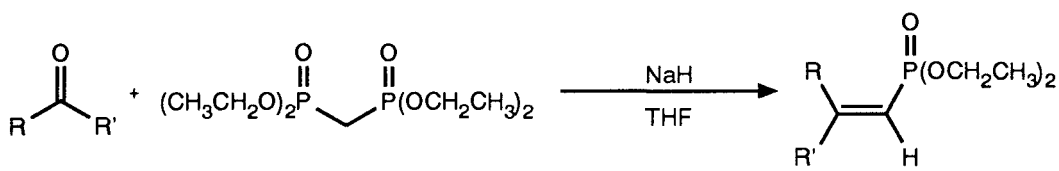
R = $CH_2CH_3$ or H

Chapter 2

# RESULTS AND DISCUSSION

The required vinyl phosphonates[35] were synthesized by a modified HWE reaction. Condensation of several representative carbonyl compounds (**61a-d**) with the anion derived from tetraethyl methylenediphosphonate (**62**)[36] afforded vinyl phosphonates (**63a-d**) in good yield.

Table I. Synthesis of vinyl phosphonates.




61 62 63

**a**, R' = $CH(CH_3)_2$; R = H

**b**, R' = $CH_2Ph$; R = H

**c**, R' = $(CH_2)_5CH_3$; R = H

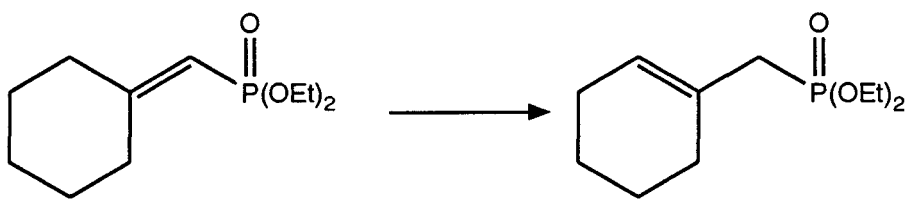
**d**, R',R = $(CH_2)_5$

| Carbonyl Compound | Yield of **63** | $^{31}P$ NMR δ |
|---|---|---|
| Isobutyraldehyde (**61a**) | 95[a] | 20.2 |
| Phenylacetaldehyde (**61b**) | 91[a] | 18.8 |
| Heptanal (**61c**) | 98[a] | 19.4 |
| Cyclohexanone (**61d**) | 54 | 18.9 |

[a](E) isomer only.

The stereochemical outcome of the synthesis of the vinyl phosphonates is worth noting. Vinyl phosphonates (**63a-c**) were shown to posses the (*E*)-configuration which was confirmed by their $^{1}H$ NMR coupling constants and $^{13}C$ NMR analysis.[43]

It is interesting that condensation of cyclohexanone (**61d**) with **62** affords solely the exocyclic olefin (**63d**). Previous attempts[37,38] to synthesize vinyl phosphonate **63d** demonstrated that the initial exocyclic double bond was readily isomerized to the endocyclic double bond (**73d**) under the reaction conditions.[39]

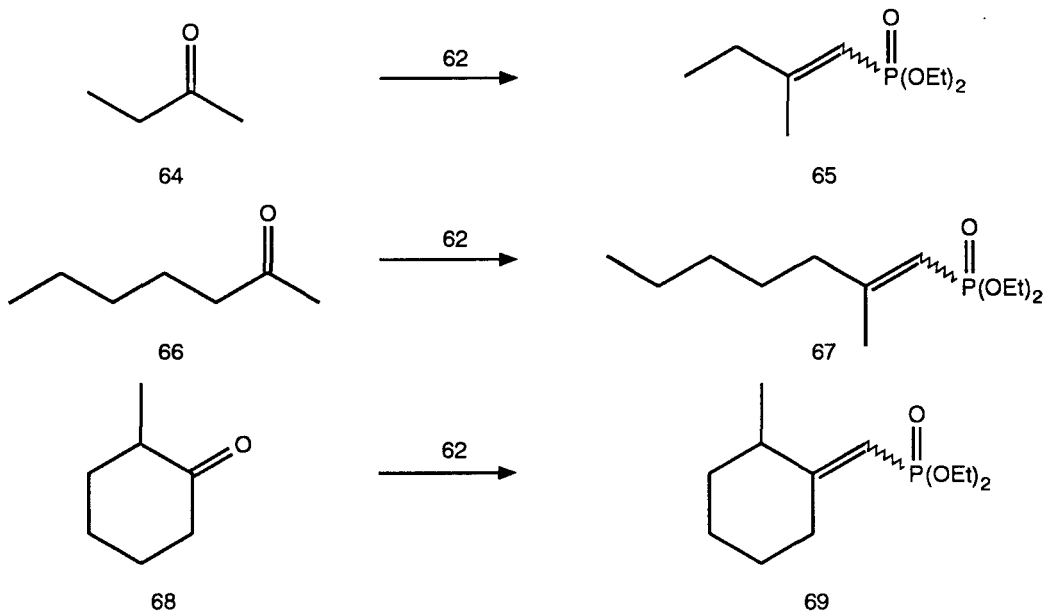



63d 73d

The $^{1}H$ and $^{13}C$ NMR shift data and coupling constants were consistent with the structure **63d**; and the $^{31}P$ chemical shift obtained for **63d** ($^{31}P$ δ 18.9) was in agreement with those obtained for vinyl phosphonates (**63a-c**) and other reported vinyl phosphonate $^{31}P$ chemical shifts.[40] The moderate yield of **63d** (54%) is also consistent with the lower reactivity of ketones in both the Wittig and HWE reactions.

Condensation of **62** with 2-butanone (**64**), 2-heptanone (**66**) and 2-methylcyclohexanone (**68**) provided the tri-substituted olefins **65**, **67**, and **69**, respectively (Scheme III).

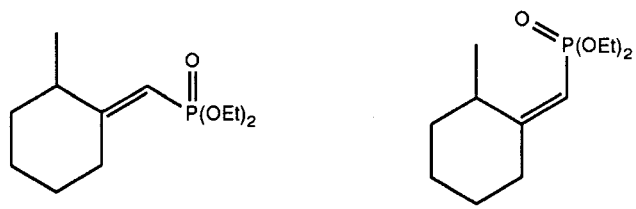
Scheme III. Vinyl phosphonate syntheses.




64 65 66 67 68 69

The trisubstituted phosphonates (**65** and **69**) could then be used to test the regio- and stereoselectivity of the isomerization of vinyl phosphonates to allylic phosphonates.

Reaction of **62** with 2-methylcyclohexanone (**68**) provides the corresponding vinyl phosphonate in 9% yield based on starting material. The $^{31}P$ NMR contained two peaks ($^{31}P$ δ 20.1, 18.8) in a 15:1 ratio consistent with the formation of the two possible stereoisomers of the vinyl phosphonate **69**.



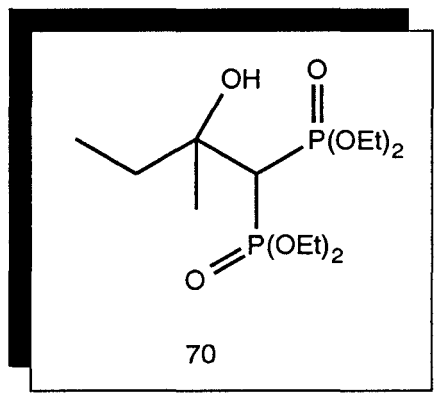

69a 69b

Attempts to separate **69a** and **69b** from starting material using flash chromatography did

not provide pure fractions of the vinyl phosphonates. Subsequent attempts to improve the yield or separate the desired vinyl phosphonates did not succeed.

The use of 2-heptanone also produced low yields of the desired vinyl phosphonate based on starting material (11%). The $^{31}P$ NMR also contained two peaks ($^{31}P$ δ 20.0, 19.2) again consistent with both the (*E*)- and (*Z*)-configuration of the vinyl phosphonate (**67**). Attempted purification did not furnish any separation of starting ketone and vinyl phosphonate.

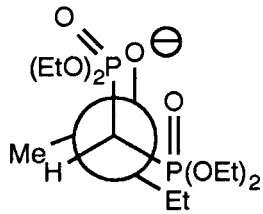
The use of 2-butanone (**64**) as the carbon electrophile gives rise to four peaks in the $^{31}P$ NMR ($^{31}P$ δ 20.4, 20.0, 19.5, 18.8). The peaks at δ 20.4 and 19.5 in the $^{31}P$ NMR were assigned the (*E*)- (*Z*)-mixture of the desired vinyl phosphonate, while those at δ 20.0 and 18.8 arise from the diastereomeric pair of β-hydroxy bis-phosphonates (**70**) the intermediate formed in the HWE reaction.



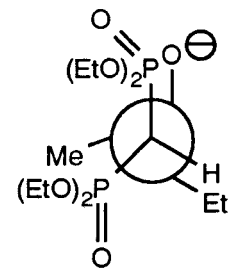

70

There are four pieces of evidence that support the structural assignment of compound **70**. The intermediate formed from attack of **62** on 2-butanone (**64**) provides the oxyanion that usually arranges itself *cis* to a phosphonate group to undergo elimination to the alkene and phosphate anion. In both cases when one of the

phosphonate groups of **62** is *cis* to the oxyanion, the other is in a highly, energetically unfavorable conformation (**71**, **72**).




71



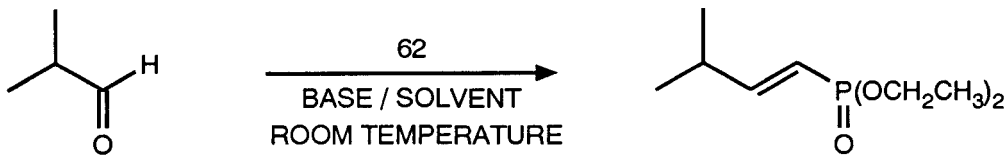

72

Both conformations required for the formation of the alkene are of high energy, eclipsing of the phosphonate and alkyl group extend the lifetime of the gauche rotomers of the intermediate which are both unsuitable for *cis*-elimination. This resulted in protonation of the intermediate oxyanion upon work-up giving the β-hydroxy bis-phosphonate. The $^{1}H$ NMR also shows a doublet of triplets with a large (20.8, 3.4 Hz) coupling constant at δ 2.6 ppm suggesting a hydrogen flanked by two phosphonate groups. There are two additional facts that support the assignment given to structure **70**. First, the $^{31}P$ NMR shifts are consistent with those assigned for other β-hydroxy phosphonates.[40,41] Second, in an attempt to isomerize the reaction mixture using $KOC(CH_3)_3$ in DMSO the $^{31}P$ NMR peaks at δ 20.4 and 19.5 are replaced by peaks downfield, while the two peaks at δ 20.0 and 18.8 remain. This would be consistent with the fact that added base did not produce an isomerization reaction of **70**.

In a effort to maximize the yield of vinyl phosphonates **63a-d**, the condensation of isobutyraldehyde (**61a**) with tetraethyl methylenediphosphonate (**62**) was examined

using several representative bases. As illustrated in Table II, use of NaH in tetrahydrofuran (THF) afforded the highest yield of the desired product.

Table II. Conditions for synthesis of vinyl phosphonates.




61a 63a

| Base | Solvent | Yield |
|---|---|---|
| NaH | THF | 95 |
| $NaOCH_2CH_3$ | THF | 47 |
| $(CH_3)_3COK$ | THF | 26 |
| $K_2CO_3$ | THF | 38 |
| $K_2CO_3$ | DMSO | 18 |

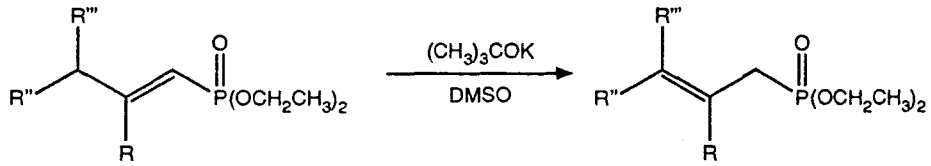
Villiras and co-workers[42] reported an 89% yield of **63a** using heterogenous reaction conditions ($K_2CO_3$, $H_2O$, 100° C) although we obtained only 38% using the same base in THF. Use of potassium carbonate in a polar solvent such as DMSO, surprisingly, afforded a very poor yield (18%) of **63a**. This was also surprising because in THF potassium carbonate gave a 38% yield of **63a**. These results can be attributed to differing basicities of potassium carbonate in the two solvents.

In view of the tendency of allylic phosphonium salts to isomerize to the

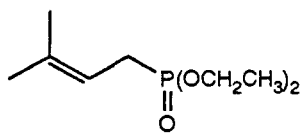
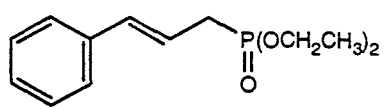
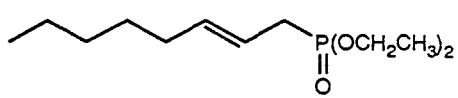
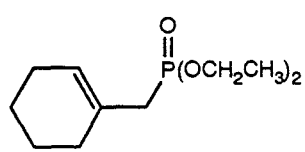
corresponding vinyl phosphonium salts in the presence of base, it was surprising to find that vinyl phosphonates (**63a-d**) isomerized exclusively to the corresponding allylic phosphonates (**73a-d**), when treated with a catalytic amount of potassium *tert*-butoxide in DMSO (Table III). The structural integrity of each isomerized product (**73a-d**) was verified by $^{31}P$ NMR analysis.

The stereochemical outcome of the isomerizations in Table III is also worth noting. All vinyl phosphonates prepared as discussed previously were shown to possess the (*E*)-configuration by $^{1}H$ NMR and $^{13}C$ NMR analysis. Spassov and co-workers[43] have shown that the $^{3}J_{C\text{-}P}$ coupling constants for vinyl phosphonates are stereodependent. The $^{3}J_{C\text{-}P}$ for *cis*-isomers is between 6.9-11.0 Hz while *trans*-isomers show 18.3-25.7 Hz coupling constants. Vinyl phosphonates (**63a-c**) showed $^{3}J_{C\text{-}P}$ coupling constants of 21.0 Hz, 23.0 Hz, 22.0 Hz, respectively, suggesting that they are of the (*E*)-configuration. In addition, $^{31}P$ NMR spectra for all vinyl phosphonates contained a single peak. The corresponding allylic phosphonates also proved to be of the (*E*)-configuration based on $^{1}H$ NMR coupling constants and $^{31}P$ NMR data. In only one of the isomerizations (**63b** → **73b**) was any (*Z*)-isomer detected in the reaction product. When **63b** was treated with a catalytic amount of potassium *tert*-butoxide at 20 °C for 5 hours, $^{1}H$ NMR analysis indicated that the corresponding allylic phosphonate was a 24/1 mixture of *E*/*Z* stereoisomers. Isolation of the major diastereomer gave a $^{1}H$ NMR spectrum identical to that of the (*E*)-isomer reported in the literature.[48] However, when the reaction time was extended to 24 hours no (*Z*)-isomer was observable by either $^{1}H$ NMR or $^{31}P$ NMR analysis.

Table III. Isomerization of vinyl phosphonates to allylic phosphonates

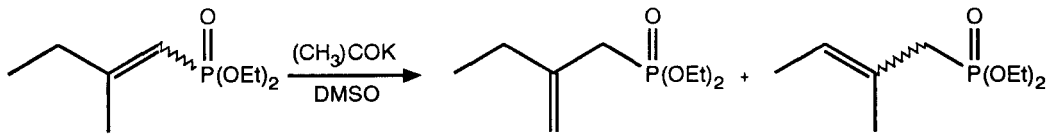



63 73

| Vinyl Phosphonate | Isomerization Product | Yield of Allylic Phosphonate (73) | $^{31}$P NMR δ |
|---|---|---|---|
| 63a |  | 85 | 29.1 |
| 63b |  | 92[a] | 27.4 (E)<br>28.7 (Z) |
| 63c |  | 66[b] | 28.5 |
| 63d |  | 84 | 28.8 |

[a] (24:1) E:Z mixture. [b] E stereoisomer only

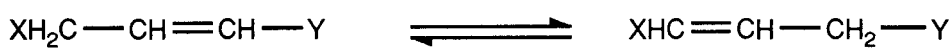
The isomerization of the vinyl phosphonate (**65**) to the allylic phosphonates **74** and **75** (as previously discussed) afforded a complex mixture of products.




65 74 75

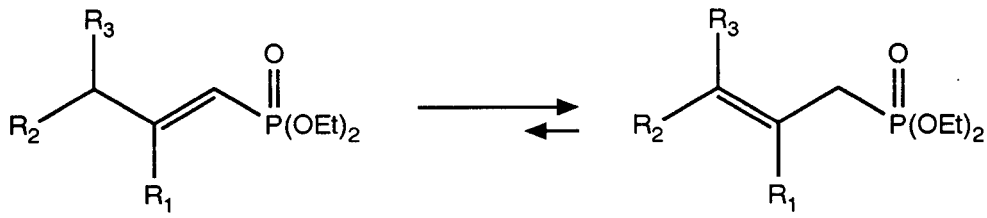
Formation of the allylic phosphonates was evidenced by the downfield appearance of three new peaks in the $^{31}P$ NMR. The $^{31}P$ NMR chemical shifts were 29.4, 29.0, 28.5 indicating the formation of **74** and the two stereoisomers of **75**.

Hine and co-workers[44] have derived the "double bond stabilization parameter" a quantitative measure of the migration of a double bond in a 1,3-disubstituted propenyl system in relation to the effect of **X** and **Y** on the stability of the alkene function.




76 77

Recently,[45] Wagener and Modro have examined the prototropic equilibrium of some diethyl alkenylphosphonates (**78**) [vinyl phosphonates] in their double bond stabilization ability. The authors found that in a t-BuOH/t-BuOK system that the equilibrium in most cases gives exclusively the allylic phosphonate (**79**).

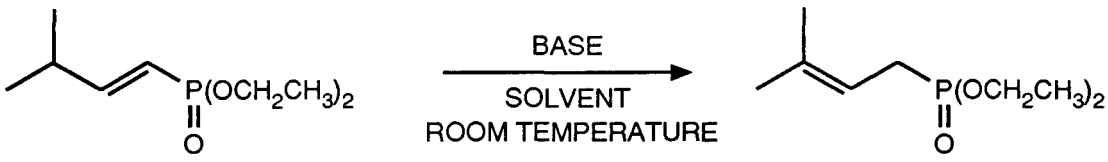



78 79

The authors showed that in their system vinyl phosphonate **63a** converts to a 99/1 mixture of allylic phosphonate (**73a**) to vinyl phosphonate (**63a**) at equilibrium. Also vinyl phosphonate (**63d**) converts exclusively to the allylic phosphonate (**73d**) at equilibrium. This data provides a theoretical explanation for our observed formation of allylic phosphonates, though the authors provide no stereochemical information for the products.

Table IV presents the results of a limited study to assess the conditions required for this isomerization. It is apparent from the yields in this study that the basicity of the *tert*-butoxide in DMSO[46] plays a crucial role in the isomerization of vinyl phosphonates to the corresponding allylic phosphonates in this investigation.

Table IV. Conditions for isomerization of allylic phosphonates.




63a 73a

| Base | Solvent | Yield |
|---|---|---|
| $(CH_3)_3COK$ | DMSO | 85 |
| $NaOCH_2CH_3$ | DMSO | 9 |
| $K_2CO_3$ | DMSO | 0 |
| $K_2CO_3$/18-Crown-6 | DMSO | 0 |
| $K_2CO_3$/18-Crown-6 | THF | 0 |

# Chapter 3

# CONCLUSION

In conclusion, we have developed a novel and reliable regio- and stereospecific synthesis of allylic phosphonates from the corresponding vinyl phosphonates. In addition to the facility with which each of the utilized transformations occurs, the exclusive formation of (*E*)-stereoisomers points to the use of the allylic phosphonates (**73**) as versatile intermediates in the stereoselective synthesis of dienes and polyenes.

Chapter 4

# EXPERIMENTAL

**General Methods.** $^{1}H$, $^{31}P$, and proton-decoupled $^{13}C$ NMR spectra were recorded at 300 MHz, 121 MHz and 75 MHz respectively. $^{1}H$ and $^{13}C$ NMR spectra were recorded in deuterated chloroform ($CDCl_3$) and all chemical shifts are referenced to tetramethylsilane (TMS) as an internal standard. $^{13}C$ NMR data includes a listing of coupling constants recorded for $^{31}P$ coupling to $^{13}C$. $^{31}P$ NMR spectra were recorded in $CDCl_3$ using 85% phosphoric acid as an external standard. Analytical thin layer chromatography (TLC) was conducted with aluminum backed silica plates. Flash chromatography was performed on Kieselgel 60, 230-400 mesh. Aldehydes were distilled directly before use, and all other solvents were purified according to standard literature procedures. The spectral properties of all vinyl and allylic phosphonates were minimally consistent with $^{1}H$ NMR data reported in the literature. When $^{13}C$ and $^{31}P$ NMR data was available for comparison, this was used as additional confirmation of the structure of products.

**General synthesis of vinyl phosphonates (63).** The ylide was generated under a nitrogen atmosphere by dropwise addition of 1.2 mmol of tetraethyl methylenediphosphonate (**62**)[36] in 2 mL THF to a stirred solution of 1.1 mmol of sodium hydride in 2 mL THF, maintained at a temperature of 15-20 °C by use of an external cold water bath. Subsequent addition of a solution of 1.0 mmol of aldehyde in 3 mL THF was

followed by stirring of this reaction mixture for an additional 0.5 h at room temperature. The mixture was then diluted with ether and extracted in successive order with 7:3(v/v) 1M aqueous NaOH:methyl alcohol (2 x 30 mL) to remove excess diphosphonate, 1:1(v/v) $H_2O$:brine (1 x 30 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo to afford the vinyl phosphonates as colorless oils after evaporative (Kugelrohr) distillation.

**General synthesis of allylic phosphonates (73).** Vinyl phosphonate (1 equiv.) and 0.25 equivalent potassium *tert*-butoxide were stirred in anhydrous dimethyl sulfoxide (2 mL per mmol of **63**) for 24 h. The mixture was subsequently diluted with ether and extracted with 10% aqueous NaCl (2 x 25 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, and the solvent removed in vacuo to afford the allylic phosphonates. Flash chromatography to separate stereoisomers of **73b** on silica (diethyl ether) afforded the pure (*E*)- and (*Z*)-**73b**.

**(*E*)-(3-Methyl-1-butenyl)phosphonic acid diethyl ester (63a):** bp 141 °C (bath temperature, 0.25 mmHg); $R_f$ = 0.73 (diethyl ether); $^1$H NMR δ 6.79 [ddd, 1H, J = 16.0, 12.3, 6.0 Hz, H-C(2)], 5.61 [m, 1H, H-C(1)], 4.09 [m, 4H, POC***H***$_2$], 2.48 [m, 1H, H-C(3)], 1.35 [t, 6H, J = 7.0 Hz, POCH$_2$C***H***$_3$], 1.08 [d, 6H, J = 6.9 Hz, CH$_3$-C(3)]; $^{13}$C NMR δ 159.7 [d, J = 4.0 Hz, C(2)], 113.0 [d, J = 188.0 Hz, C(1)], 61.6 [d, J = 5.6 Hz, PO***C***H$_2$], 32.5 [d, J = 21.0 Hz, C(3)], 21.1 [CH$_3$-C(3)], 21.0 [CH$_3$-C(3)], 16.4 [d, J = 6.4 Hz, POCH$_2$***C***H$_3$]; $^{31}$P NMR δ 20.2. $^1$H NMR data were consistent with that previously reported for this compound and confirmed the absence of the corresponding (*Z*)-stereoisomer, $^1$H NMR data of which has been published.[37,38]

**(3-Methyl-2-butenyl)phosphonic acid diethyl ester (73a):** bp 134 °C (bath temperature, 0.3 mmHg); $R_f$ = 0.67 (diethyl ether); $^1$H NMR δ 5.45 [m, 1H, H-C(2)], 4.06 [m, 4H, POC***H***$_2$], 2.53 [dd, 2H, J = 22.0, 7.2 Hz, H-C(1)], 1.74 [d, 3H, J = 5.7 Hz, $CH_3$-C(3)], 1.65 [d, 3H, J = 4.5 Hz, $CH_3$-C(3)], 1.29 [t, 6H, J = 7.0 Hz, $POCH_2C\boldsymbol{H}_3$]; $^{13}$C NMR δ 137.1 [d, J = 14.8 Hz, C(3)], 113.2 [d, J = 11.1 Hz, C(2)], 61.7[d, J = 6.7 Hz, PO***C***$H_2$], 26.4 [d, J = 140.0 Hz, C(1)], 25.7 [$CH_3$-C(3)], 17.9 [$CH_3$-C(3)], 16.4 [d, J = 6.0 Hz, $POCH_2\boldsymbol{C}H_3$]; $^{31}$P NMR δ 29.1. $^1$H, $^{13}$C and $^{31}$P NMR data were consistent with those previously reported.[18]

**(*E*)-(3-Phenyl-1-propenyl)phosphonic acid diethyl ester (63b).** bp 206 °C (bath temperature, 0.3 mmHg); $R_f$ = 0.74 (diethyl ether); $^1$H NMR δ 7.37-7.20 [m, 5H, phenyl], 6.95 [m, 1H, H-C(2)], 5.66 [dd, 1H, J = 17.4, 1.8 Hz, H-C(1)], 4.10 [m, 4H, POC***H***$_2$], 3.58 [d, 2H, J = 6.3 Hz, H-C(3)], 1.35 [t, 6H, J = 7.2 Hz, $POCH_2C\boldsymbol{H}_3$]; $^{13}$C NMR δ 151.5 [d, J = 5.3 Hz, C(2)], 138.0, 137.2, 128.8, 128.6, 128.5, 126.6, 118.1 [d, J = 187.0 Hz, C(1)], 61.7 [d, J = 5.6 Hz, PO***C***$H_2$], 40.4 [d, J = 23.0 Hz, C(3)], 16.4 [d, J = 6.3 Hz, $POCH_2\boldsymbol{C}H_3$]; $^{31}$P NMR δ 18.8. $^1$H NMR data were consistent with that previously reported.[47]

**(*E*)-(3-Phenyl-2-propenyl)phosphonic acid diethyl ester (73b):** bp 221 °C (bath temperature, 0.05 mmHg); $R_f$ = 0.71 (diethyl ether); $^1$H NMR δ 7.40-7.20 [m, 5H, phenyl], 6.55 [dd, 1H, J = 16.0, 5.3 Hz, H-C(3)], 6.18 [m, 1H, H-C(2)], 4.17 [m, 4H, POC***H***$_2$], 2.79 [ddd, 2H, J = 22.0, 7.5, 1.3 Hz, H-C(1)], 1.34 [t, 6H, J = 6.3 Hz, $POCH_2C\boldsymbol{H}_3$]; $^{13}$C NMR δ 136.7, 134.5 [d, J = 15.0 Hz, C(3)], 128.6, 128.5, 128.1, 127.5, 126.1, 118.7 [d, J = 12.0 Hz, C(2)], 62.2 [d, J = 6.6 Hz, PO***C***$H_2$], 31.0 [d, J = 140.0 Hz,

C(1)], 16.5 [d, J = 6.0 Hz, $POCH_2\mathit{C}H_3$]; $^{31}P$ NMR δ 27.4. $^1H$ NMR data were consistent with that previously reported for the (*E*)-isomer.[48]

**(*Z*)-(3-Phenyl-2-propenyl)phosphonic acid diethyl ester (73b)**: bp 219 °C (bath temperature, 0.1 mmHg); $R_f$ = 0.68 (diethyl ether); $^1H$ NMR δ 7.31 [m, 5H, phenyl], 6.56 [dd, 1H, J = 13.4, 4.8 Hz, H-C(2)], 6.20 [m, 1H, H-C(3)], 4.15 [m, 4H, $POC\mathit{H}_2$], 3.88 [m, 1H, H-C(1)], 3.61 [m, 1H, H'-C(1)], 1.37 [t, 6H, J = 5.8 Hz, $POCH_2C\mathit{H}_3$]; $^{13}C$ NMR δ 132.7, 129.7 [d, J = 28.1 Hz, C(3)], 128.6, 128.5, 127.3, 126.2, 126.1, 104.1 [C(2)], 63.8 [$PO\mathit{C}H_2$], 28.6 [d, J = 202.2 Hz, C(1)], 16.5 [d, J = 6.0 Hz, $POCH_2\mathit{C}H_3$]; $^{31}P$ NMR δ 28.7. $^1H$ NMR data were consistent with that previously reported.[26]

**(*E*)-1-Octenylphosphonic acid diethyl ester (63c)**: bp 171 °C (bath temperature, 0.4 mmHg); $R_f$ = 0.79 (diethyl ether); $^1H$ NMR δ 6.80 [ddd, 1H, J = 17.1, 11.0, 5.0 Hz, H-C(2)], 5.65 [dd, 1H, J = 18.7, 4.1 Hz, H-C(1)], 4.08 [m, 4H, $POC\mathit{H}_2$], 2.22 [m, 2H, H-C(3)], 1.45 [m, 2H], 1.34 [t, 6H, J = 7.1 Hz, $POCH_2C\mathit{H}_3$], 1.31 [m, 6H], 0.90 [t, 3H, J = 7.0 Hz, H-C(8)]; $^{13}C$ NMR δ 153.8 [d, J = 4.4 Hz, C(2)], 116.6 [d, J = 187.4 Hz, C(1)], 61.5 [d, J = 5.5 Hz, $PO\mathit{C}H_2$], 34.2 [d, J = 22.0 Hz, C(3)], 31.3, 27.5, 27.4, 22.4, 16.4 [d, J = 6.4 Hz, $POCH_2\mathit{C}H_3$], 14.0 [C(8)]; $^{31}P$ NMR δ 19.4. $^1H$ NMR data were consistent with that previously reported.[49]

**(*E*)-2-Octenylphosphonic acid diethyl ester (73c)**: bp 163 °C (bath temperature, 0.3 mmHg); $R_f$ = 0.69 (diethyl ether); $^1H$ NMR δ 5.59 [m, 1H, vinyl-H], 5.41 [m, 1H, vinyl-H], 4.10 [m, 4H, $POC\mathit{H}_2$], 2.54 [ddd, 2H, J = 19.5, 6.8, 4.8 Hz, H-C(1)], 2.04 [m, 2H], 1.32 [m, 6H], 1.31 [t, 6H, J = 7.1 Hz, $POCH_2C\mathit{H}_3$], 0.90 [t, 3H, J = 7.0 Hz, H-C(8)]; $^{13}C$ NMR δ 136.1 [d, J = 17.0 Hz, C(3)], 118.5 [d, J = 13.4 Hz, C(2)], 61.9 [d, J = 6.7

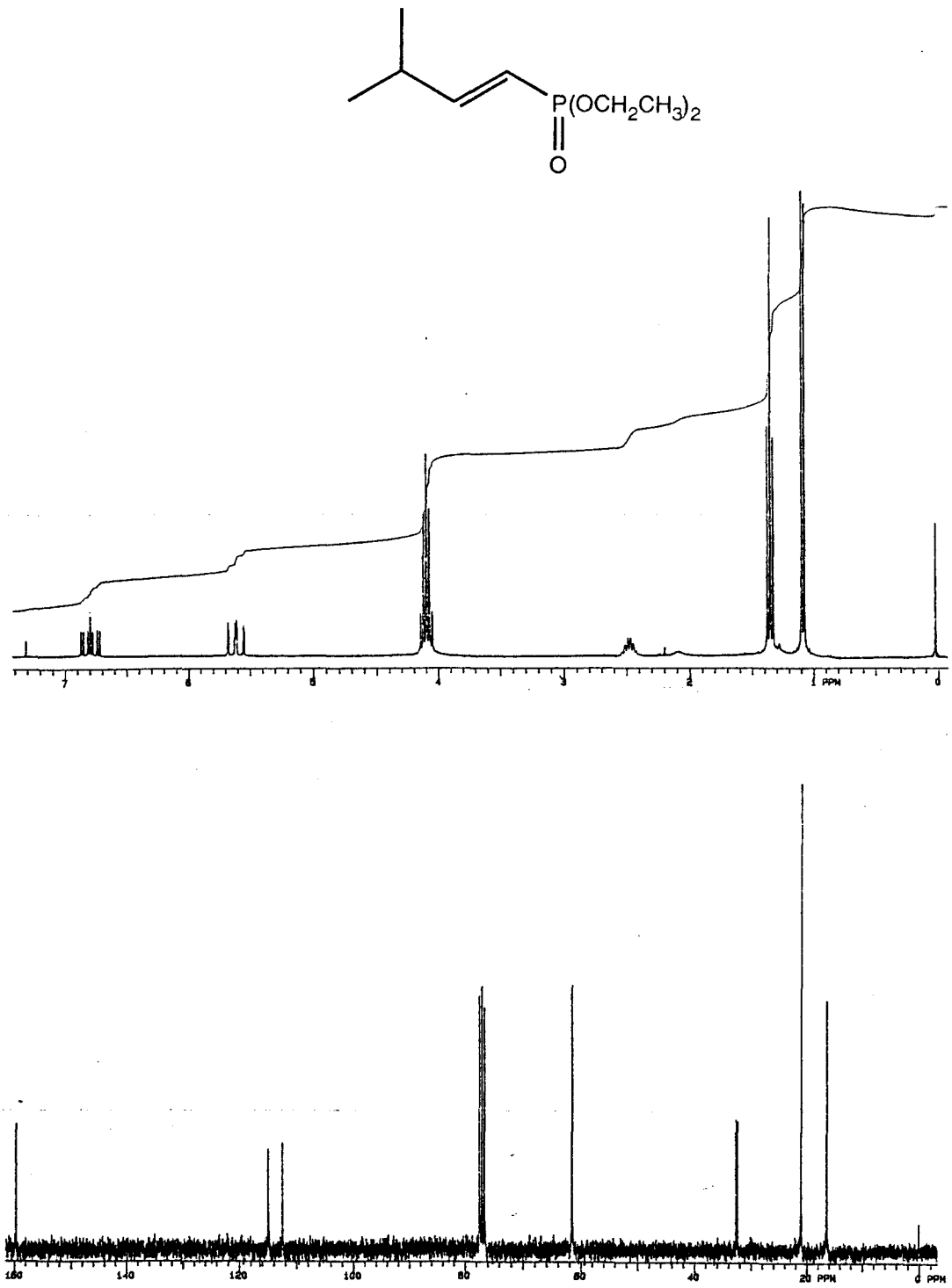
Hz, PO*C*$H_2$], 34.7, 30.6 [d, J = 146.0 Hz, C(1)], 27.5, 27.4, 22.2, 16.4 [d, J = 6.5 Hz, POC$H_2$*C*$H_3$], 13.7 [C(8)]; $^{31}$P NMR δ 28.5. $^1$H NMR data were consistent with that previously reported.[50]

**(Cyclohexylidenemethyl)phosphonic acid diethyl ester (63d):** bp 169 °C (bath temperature, 0.5 mmHg); $R_f$ = 0.63 (diethyl ether); $^1$H NMR δ 5.36 [d, 1H, J = 21.0 Hz, *CH*P], 4.10 [m, 4H, POC*H*$_2$], 2.65 [m, 2H], 2.27 [m, 2H], 1.71 [m, 6H], 1.35 [t, 3H, J = 7.0 Hz, POCH$_2$C*H*$_3$]; $^{13}$C NMR δ 167.8 [d, J = 3.0 Hz], 109.2 [d, J = 152.0 Hz, C(1)], 61.3 [d, J = 6.9 Hz, PO*C*H$_2$], 39.1 [d, J = 24.0 Hz], 32.2 [d, J = 17.6 Hz], 28.7, 28.0, 25.9, 16.4 [d, J = 6.2 Hz, POCH$_2$*C*H$_3$]; $^{31}$P NMR δ 18.9. HRMS, calcd. for $C_{11}H_{21}O_3P$ 232.1228, found 232.1228. $^1$H NMR data were consistent with that previously reported.[45]

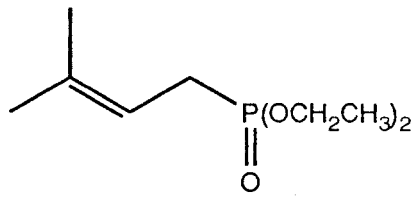
**[(1-Cyclohexenyl)methyl]phosphonic acid diethyl ester (73d):** bp 174 °C (bath temperature, 0.3 mmHg); $R_f$ = 0.81 (diethyl ether); $^1$H NMR δ 5.61 [m, 1H, vinyl-H], 4.10 [m, 4H, POC*H*$_2$], 2.50 [d, 2H, J = 24.0 Hz, C*H*$_2$P], 2.11 [m, 4H], 1.58 [m, 4H], 1.31 [t, 6H, J = 7.6 Hz, POCH$_2$C*H*$_3$]; $^{13}$C NMR δ 135.0 [d, J = 13.0 Hz], 126.5 [d, J = 10.7 Hz], 61.8 [d, J = 6.6 Hz, PO*C*H$_2$], 39.1, 32.1 [d, J = 162.0 Hz, C(1)], 29.5, 22.9, 22.0, 16.5 [d, J = 6.1 Hz, POCH$_2$*C*H$_3$]; $^{31}$P NMR δ 28.8. HRMS, calcd for $C_{11}H_{21}O_3P$ 232.1228, found 232.1224. $^1$H NMR and $^{31}$P NMR data were consistent with that previously reported.[37,38,45]

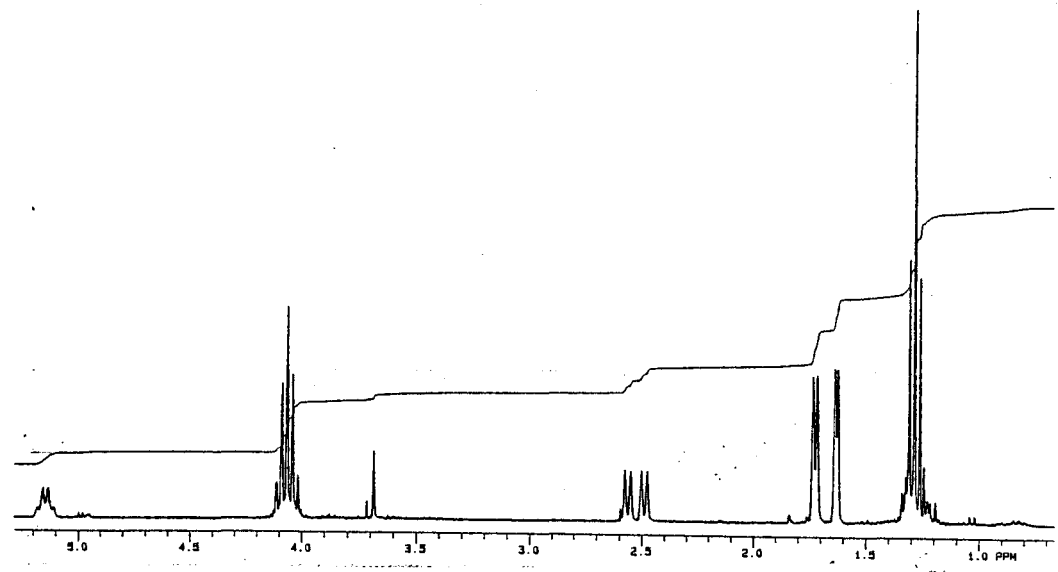
# APPENDIX

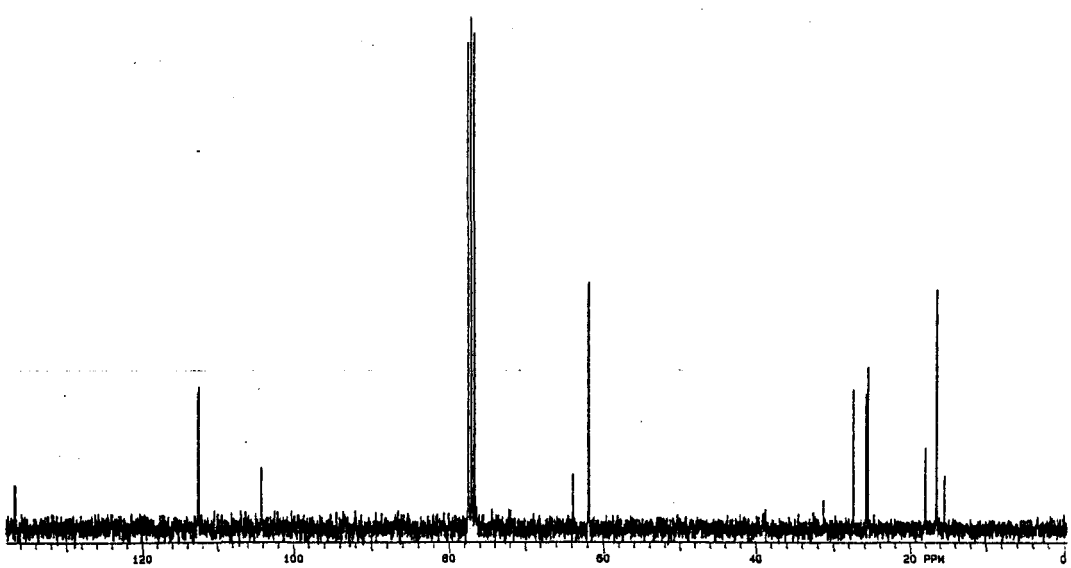
# SPECTRAL DATA



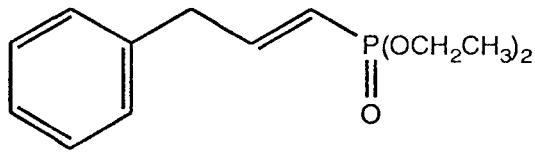

$^{1}$H NMR and $^{13}$C NMR (*E*)-(3-Methyl-1-butenyl)phosphonic acid diethyl ester (**63a**)

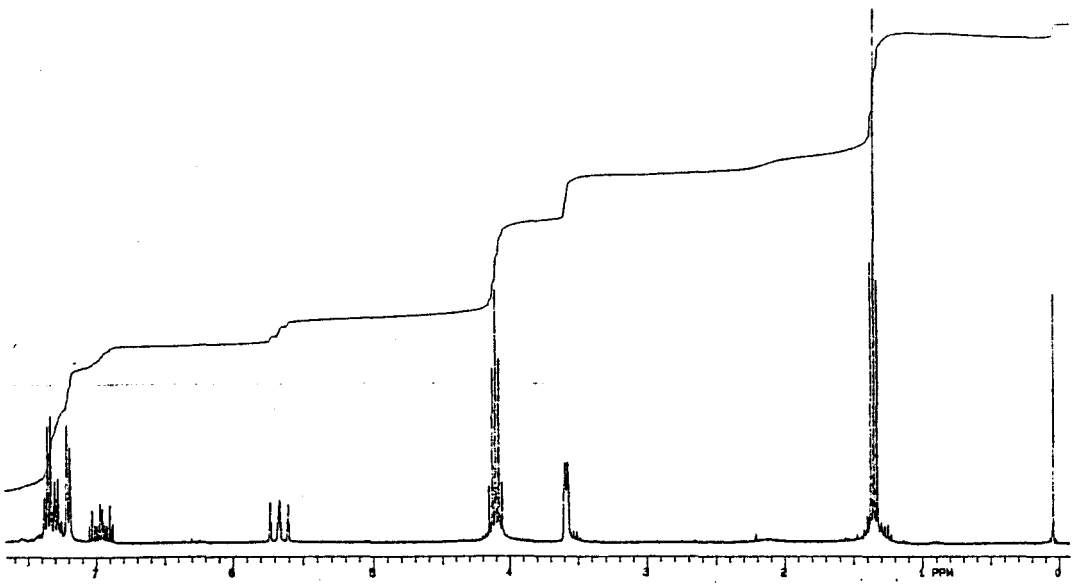


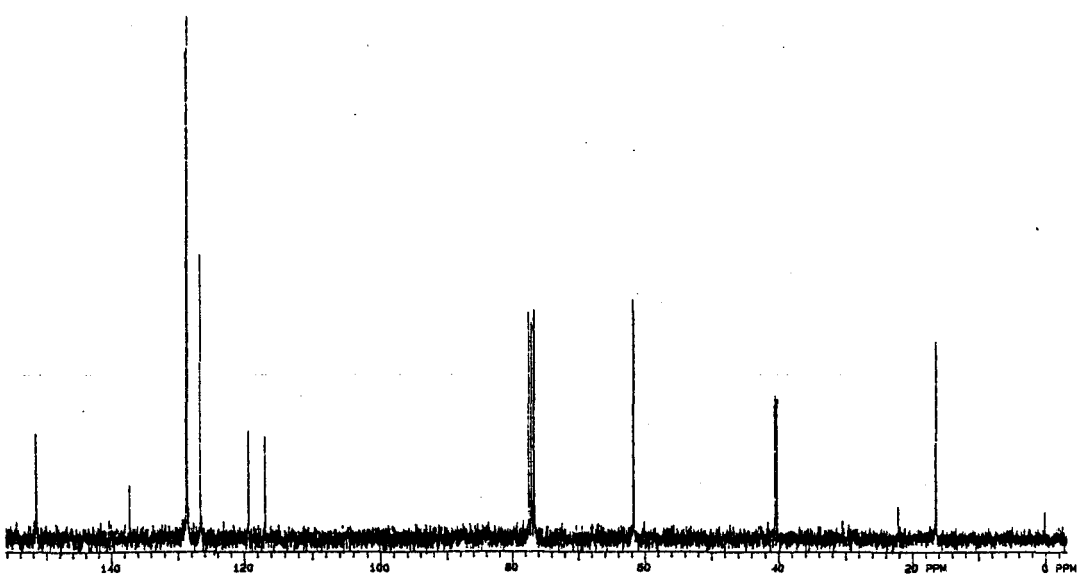




$^{1}$H NMR and $^{13}$C NMR (3-Methyl-2-butenyl)phosphonic acid diethyl ester (**73a**)

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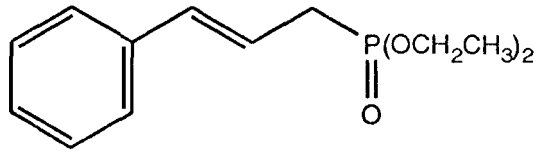
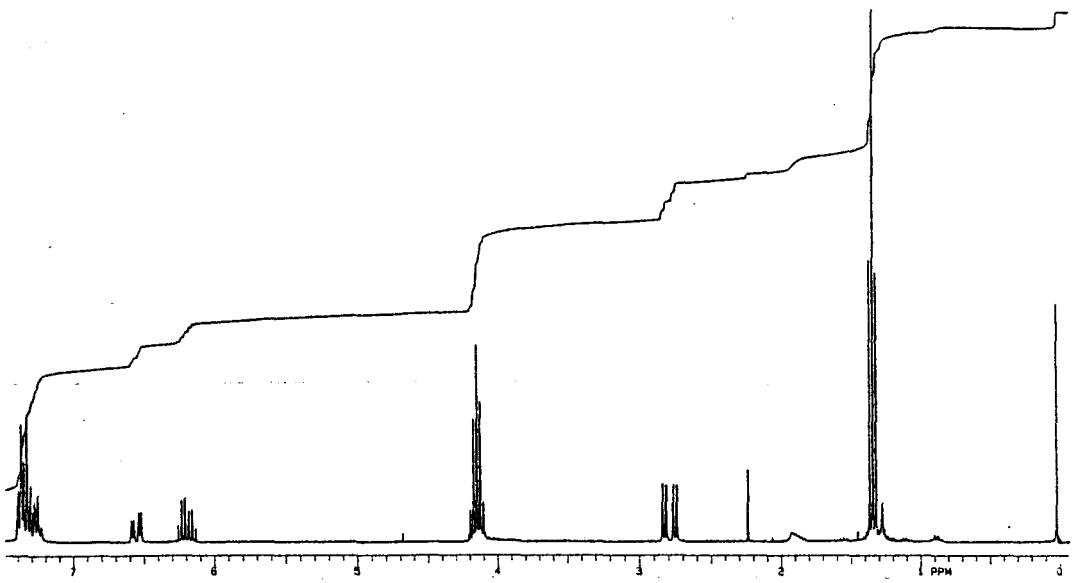
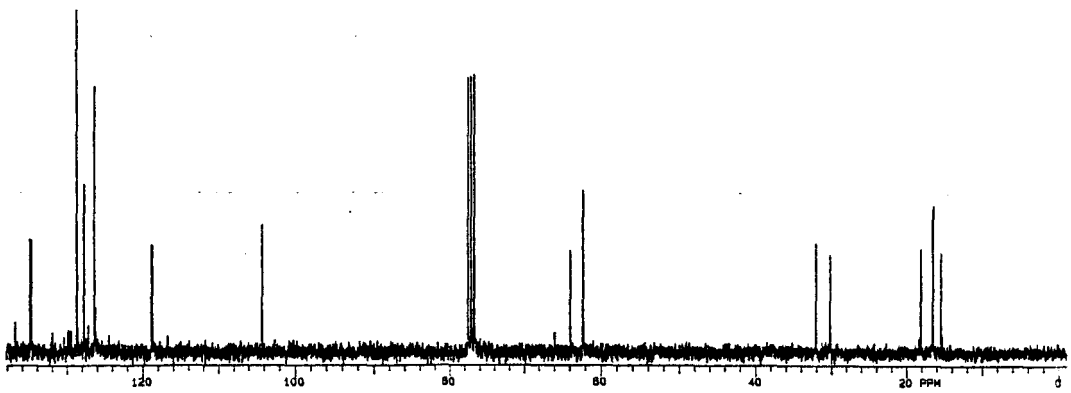
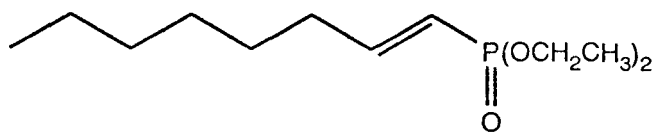
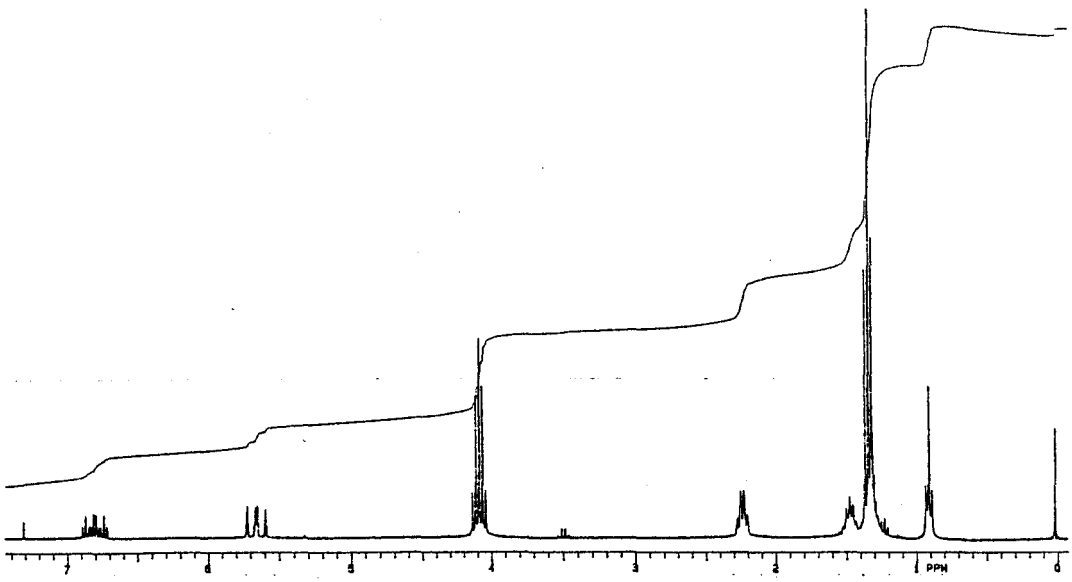


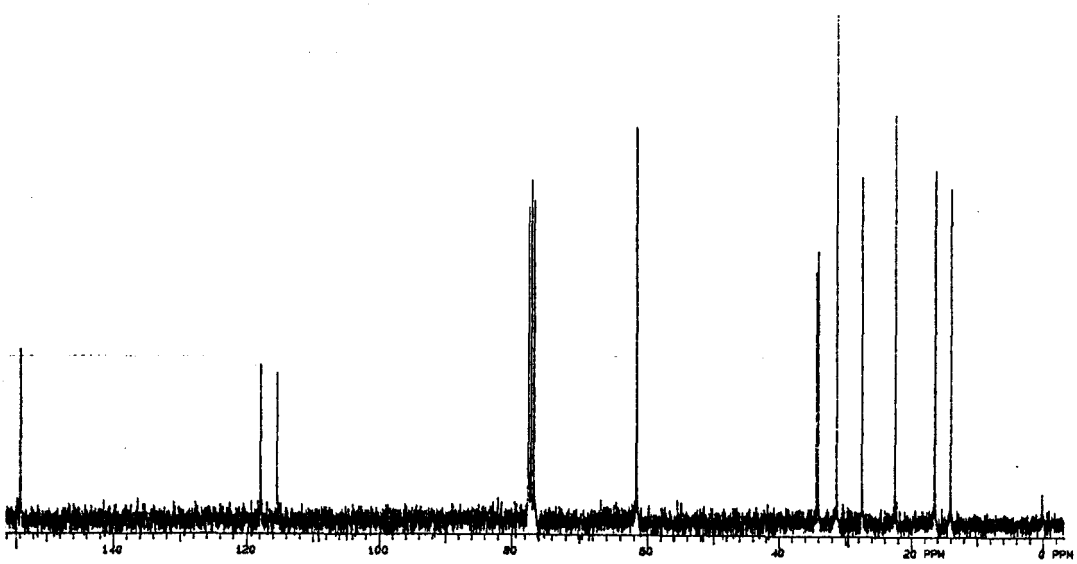



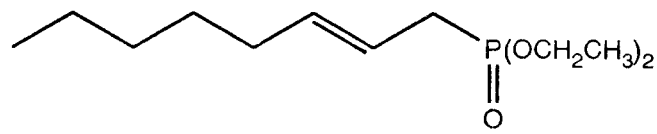

$^{1}$H NMR and $^{13}$C NMR (*E*)-(3-Phenyl-2-propenyl)phosphonic acid diethyl ester (**73b**)

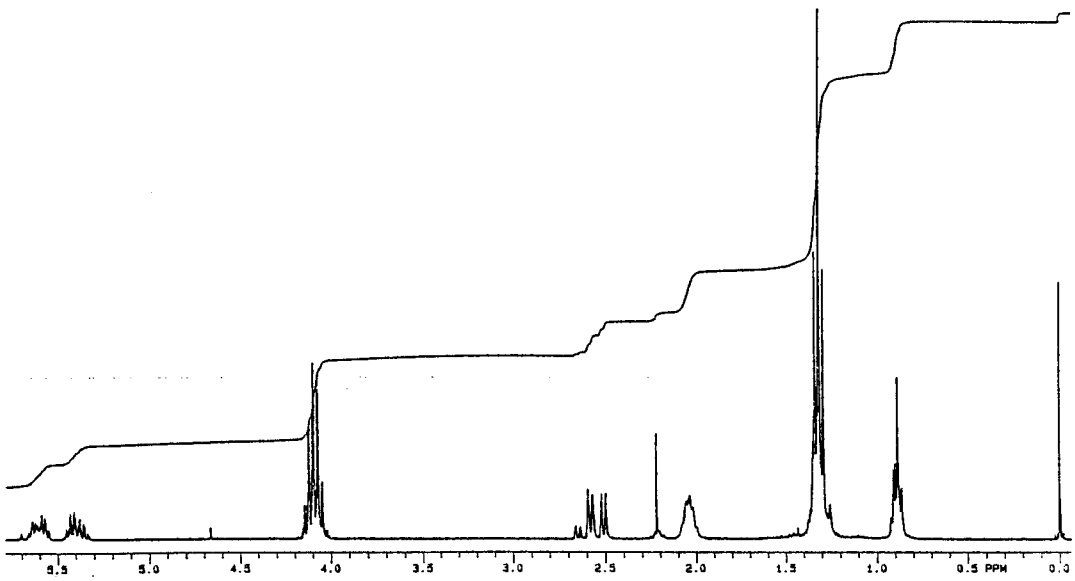


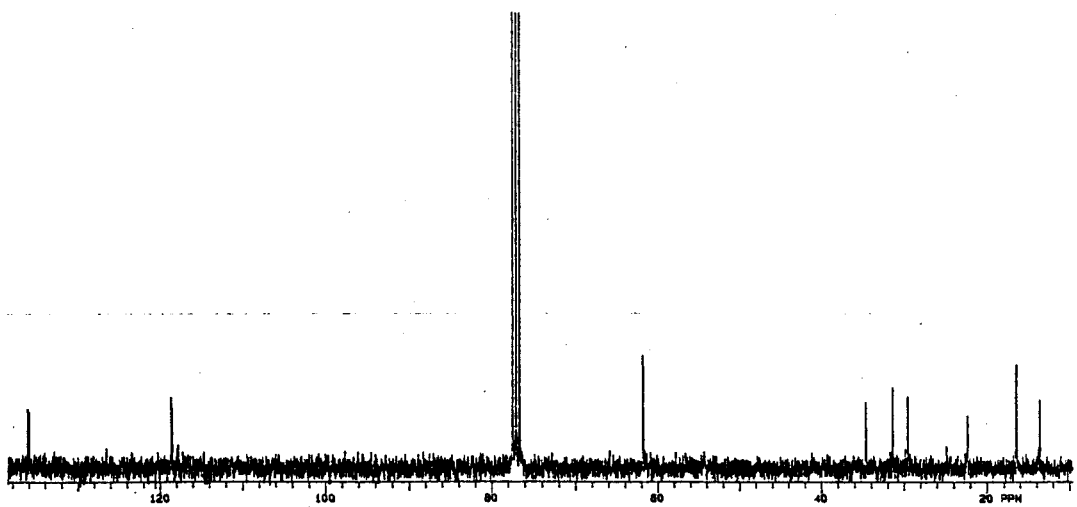




$^{1}$H NMR and $^{13}$C NMR (*E*)-1-octenylphosphonic acid diethyl ester (**63c**)

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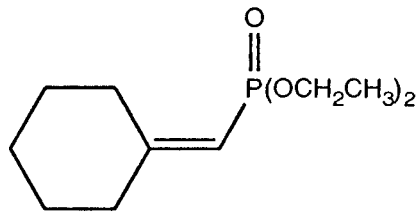
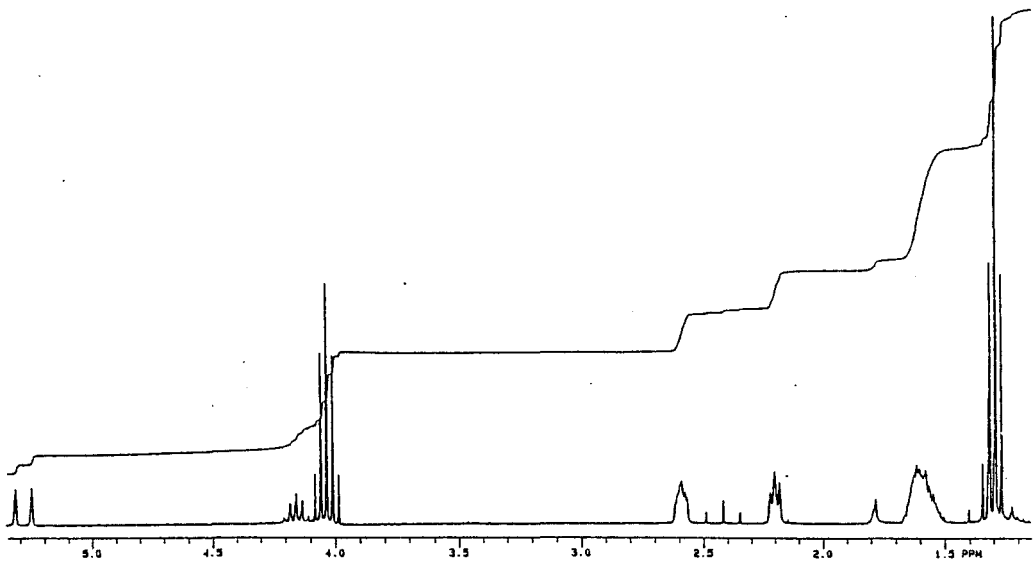
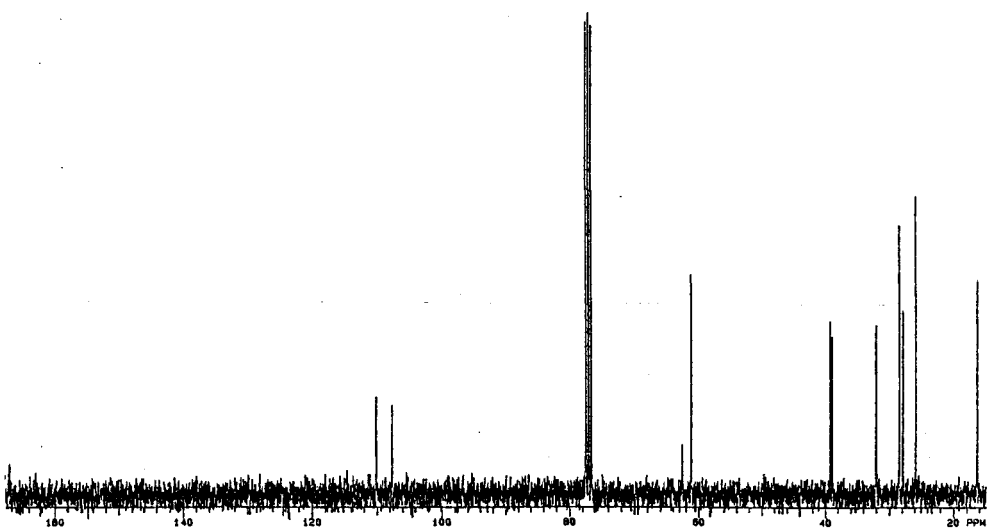
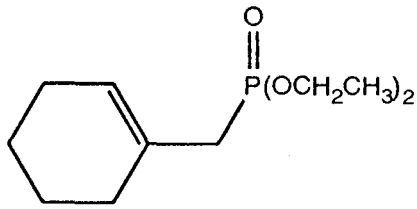
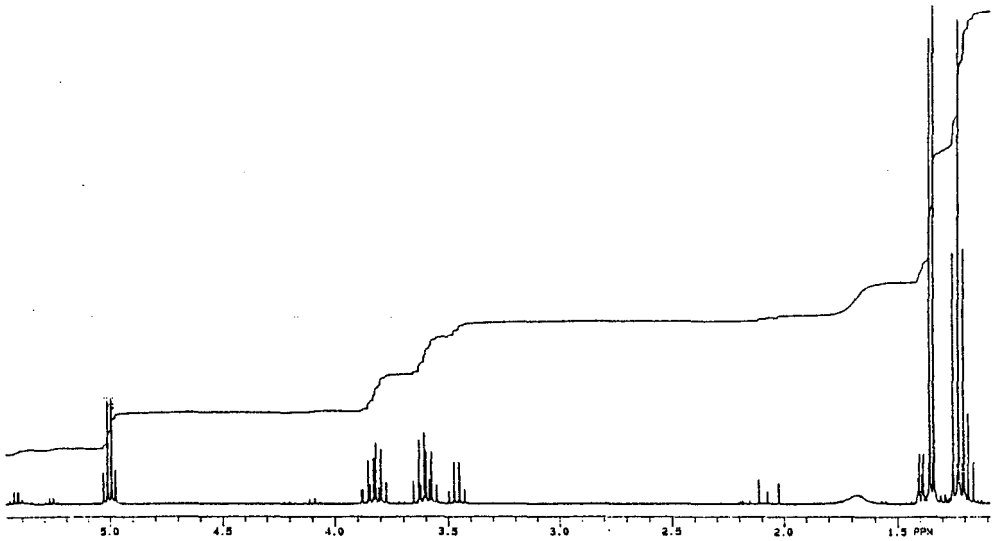


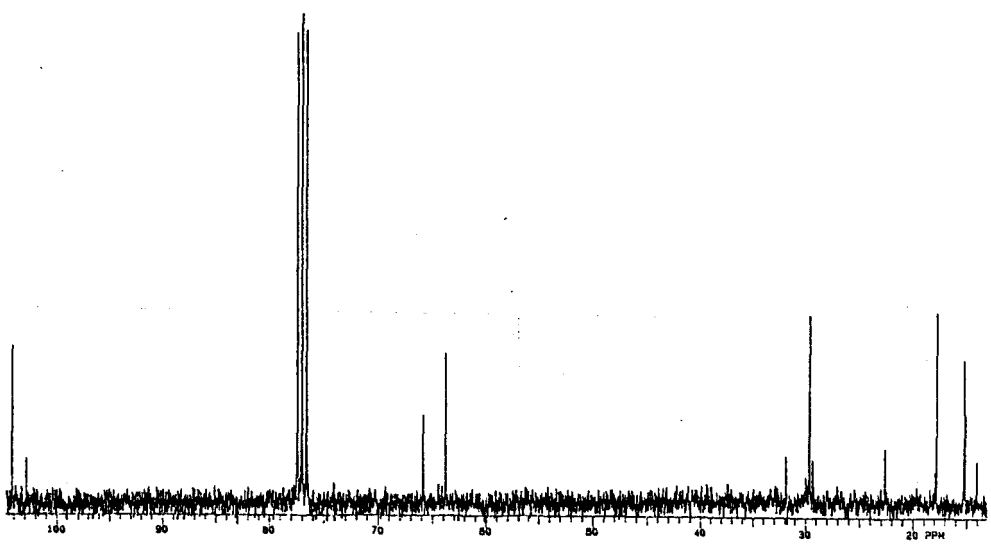




$^{1}$H NMR and $^{13}$C NMR (Cyclohexylidenemethyl)phosphonic acid diethyl ester (**63d**)




$^{1}H$ NMR and $^{13}C$ NMR [(1-Cyclohexenyl)methyl]phosphonic acid diethyl ester (**73d**)

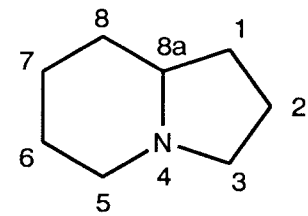
# PART II

Chapter 5

# INTRODUCTION

## The Indolizidine Alkaloids

The 1-azabicyclo[4.3.0]nonane skeleton (indolizidine) represents a diverse group of compounds isolated from both plant and animal sources. A recent review of the literature showed that 25 to 30% of the known alkaloids incorporate the indolizidine skeleton in various forms.[51] The accepted numbering convention for the 1-azabicyclo[4.3.0]nonane skeleton is indicated below.

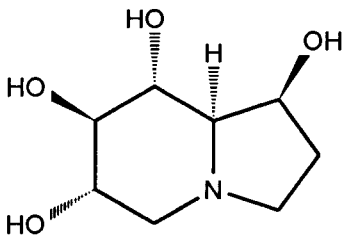


1-Azabicyclo[4.3.0]nonane

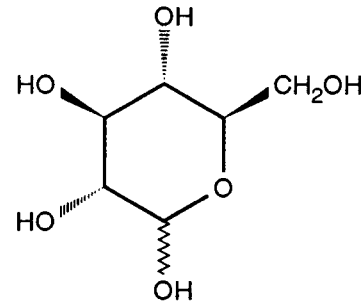
δ-Coniceine, also known as octahydropyrrocoline or indolizidine, is the parent nucleus to a diverse group of alkaloids both structurally and biologically. An overview of the major classes of indolizidine alkaloids will be discussed.

Castanospermine and swainsonine[52,53] represent the class of polyhydroxylated indolizidine alkaloids. Both molecules are potent glycosidase inhibitors owing to the fact that their structures share common features with glucose and mannose, respectively.[54] Of

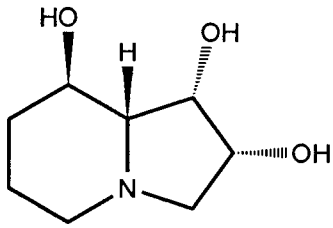
all the simple indolizidine alkaloids, castanospermine and swainsonine are the most thoroughly studied both synthetically and biologically. Swainsonine shows immunomodulator ability and use in cancer chemotherapy.[55] Castanospermine is a potent inhibitor of glycoprotein processing, which opens application as an antitumor agent,[56-60] antiviral[61-65] and especially use as anti-HIV agents.[66,67]



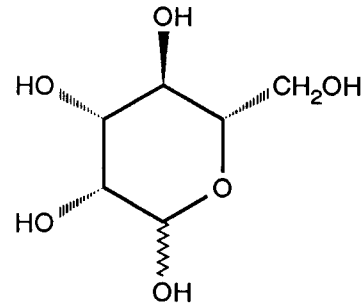

Castanospermine




D-Glucose

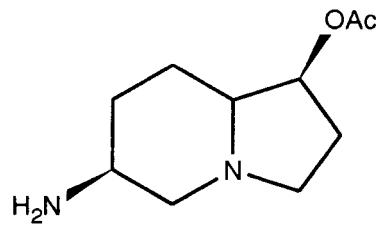



Swainsonine



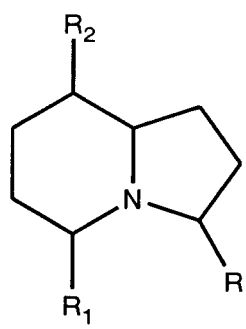

D-Mannose

Slaframine[52] is an indolizidine that has an unusual substitution pattern, and is the etiologic agent of slobber syndrome in dairy cattle. It also has been used as a therapeutic agent for the treatment of symptoms of cystic fibrosis.[68]




Slaframine

Among the most interesting and diverse class of the simple indolizidine alkaloids are those isolated from amphibians. The indolizidines (formerly the gephyrotoxins)[69] contain alkyl chains substituted in a variety of patterns at the 3, 5 and 8 position of the 1-azabicyclo[4.3.0]nonane skeleton.




R = H or Alkyl
$R_1$ = H or Alkyl
$R_2$ = H or Methyl

Indolizidines

The first molecules isolated in this class contained hydrocarbon chains at the 3 (R) and 5 ($R_1$) positions of the indolizidine nucleus. As more molecules were isolated some were found to contain sites of unsaturation and hydroxylation in the chains at the 3 and 5-position. These molecules are also considered as compounds in this class of

indolizidine alkaloids. The indolizidines (gephyrotoxins) have received considerably less attention than other indolizidine alkaloids, but represent challenging target molecules for synthetic chemists.

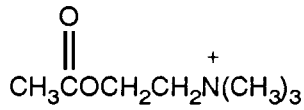
The focus of this dissertation will be on the preparation of indolizidines and methods for substitution at the 3, 5 and 8-position in the indolizidine ring system.

Isolation and Biological Activity

The indolizidines are isolated in minute quantities from the skin of neotropical frogs of the genus *Dendrobatidae*.[70-76] The frogs secrete the indolizidine alkaloids as a natural defense under stress. These skin secretions have been used as arrow poisons by South American natives for decades.

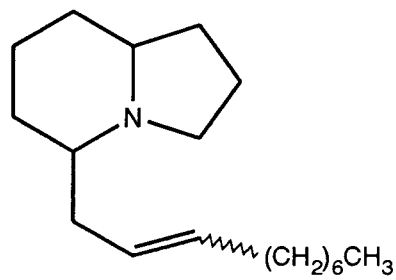
The characterization of these alkaloids has been extensively reviewed. The indolizidines are classified numerically, with values associated to their nominal molecular weight as determined by mass spectral analysis (e.g. **223**). When other alkaloids of the same nominal molecular weight are identified, letters are attached to each to distinguish specific substitution patterns and stereochemistry (e.g. **223** becomes **223A** and **223B**).[70]

Because of the small amounts isolated from the natural sources very little is known concerning their biological activities. In early investigations, Daly and co-workers[77] showed that indolizidines inhibit the acetylcholine receptor, and are weak antagonists of muscarinic receptors. Daly and co-workers[78] also have shown that the indolizidines are moderately active inhibitors of the nicotinic acetylcholine receptor ion channel in electric eels. More recently, Daly[70] has shown that the 3,5-disubstituted indolizidines produce long lasting locomotor difficulties following subcutaneous injections in mice. In addition, it has also been shown that the inhibition of nicotinic acetylcholine receptor ion channels is universal for all indolizidine substitution patterns.[70] The receptor blocking ability of the indolizidines is probably associated with protonation of the tertiary amine at physiological pH. The resulting quarternary ammonium salt would be structurally related to the ammonium salt portion of acetylcholine.



Acetylcholine

Recently, a 5-substituted indolizidine has been isolated from a previously unknown source: a sea tunicate *Clavelina Picta.*[83] Piclavine A contains a dec-2-enyl chain at the 5-position of the indolizidine nucleus.

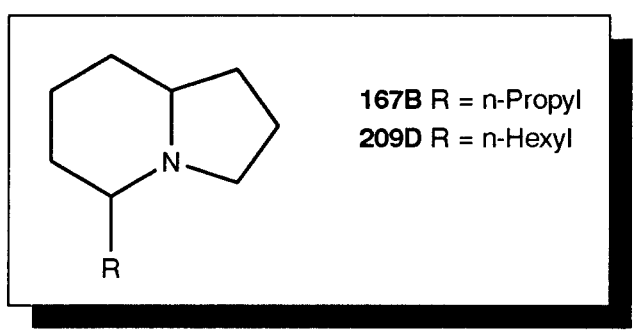


Piclavine A

Previous Syntheses

Synthetic strategies for the preparation of the indolizidines in both racemic and optically active forms have been the subject of many recent reports. Several excellent reviews covering the syntheses of compounds of this class are available, with updated reports appearing regularly in several sources.[79-82] In this section, indolizidines that either have been prepared or can be easily accessed from the intermediates in this dissertation will be reviewed. This section is further divided into common substitution patterns (5-, 3,5- and 5,8-) that are common to the natural indolizidines.

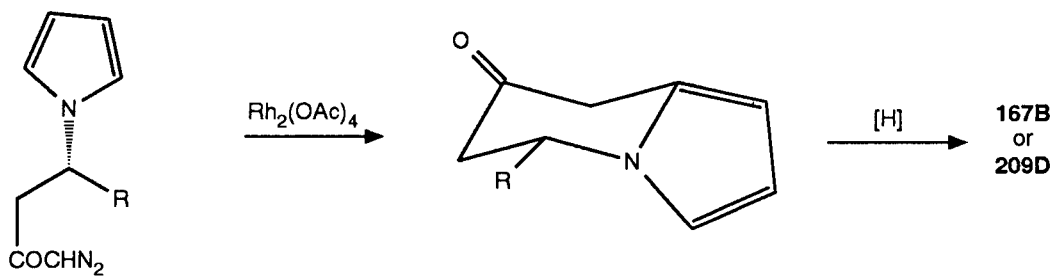
Indolizidines **167B** and **209D** represent the simplest of the substitution patterns where there is a sole alkyl group at the 5-position in the nucleus.




Jefford and Wang[84] carried out an enantiospecific synthesis of **167B** and **209D** using a rhodium(II) acetate catalyzed decomposition of an intermediate diazo-compound (**1**) as a key step followed by hydrogenation (Scheme IV). Polniaszek and Belmont[85] reported the enantioselective synthesis of **167B** and **209D** via alkylation of a common amino-nitrile

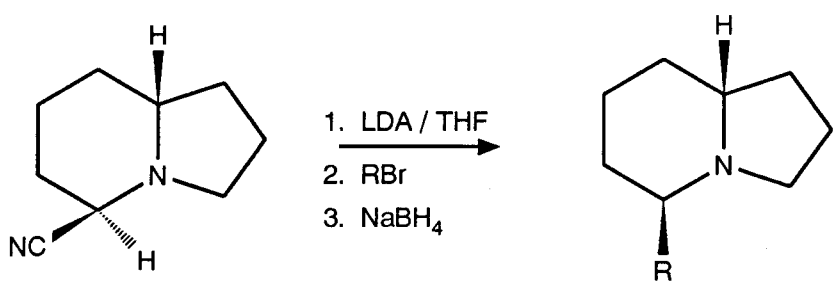
intermediate (**3**) (Scheme V).

Scheme IV. Jefford synthesis of indolizidine **106B** and **209D**.



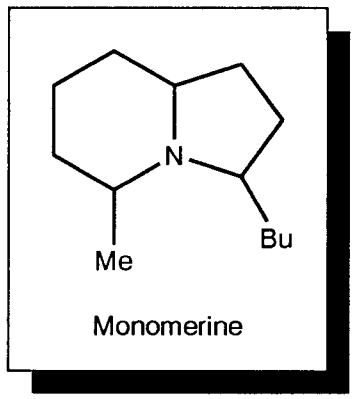

1 2

Scheme V. Polniaszek synthesis of indolizidine **106B** and **209D**.




3

Monomerine, a member of the 3,5-substituted indolizidines, has been the focus of a large amount of synthetic work. Monomerine is the trail pheromone of the pharaoh ant *Monomorium Pharaonis.*

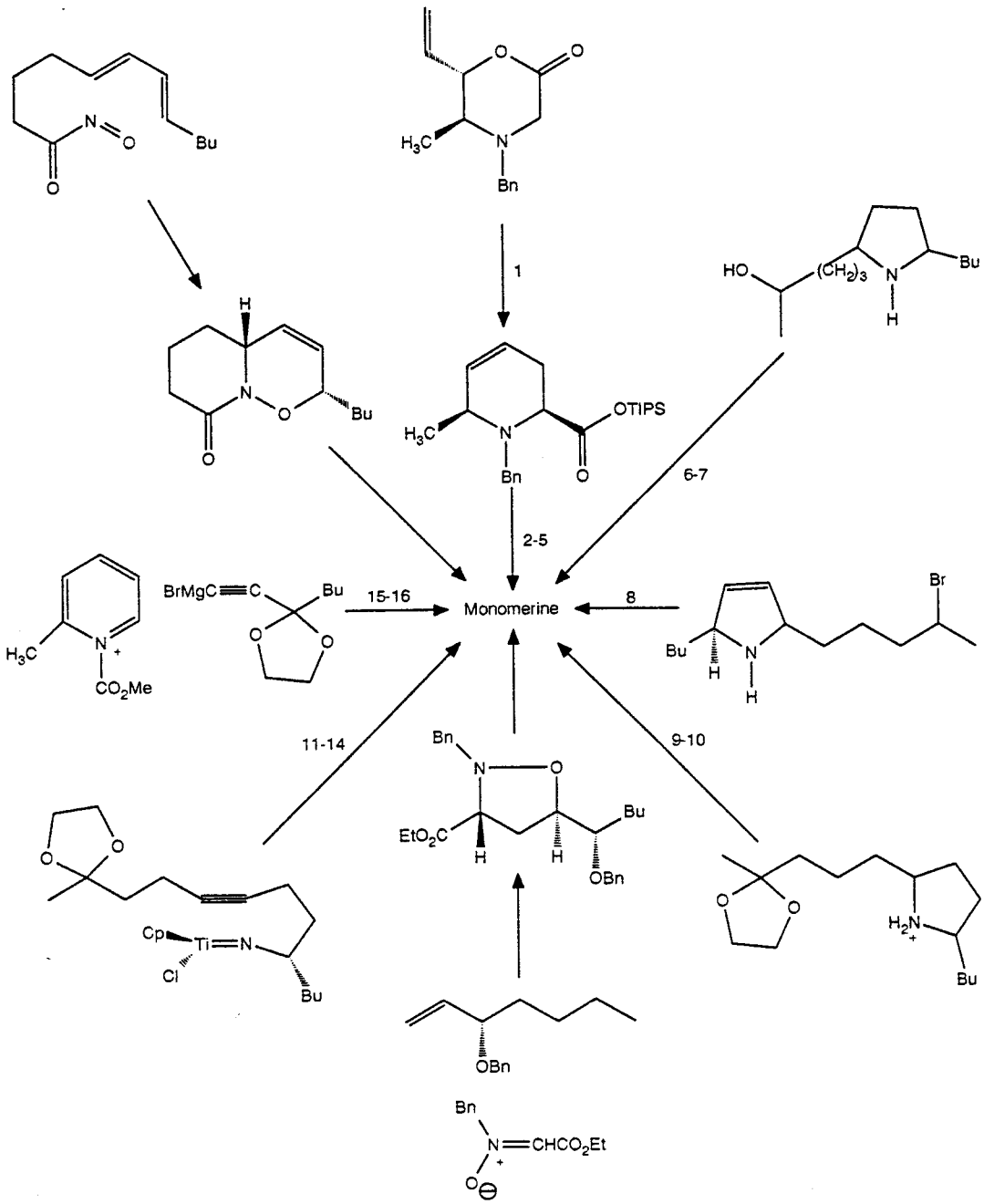



Monomerine

Although monomerine is not of amphibian origin it is classified with the other indolizidines owing to structural similarity. Also, synthetic strategies toward monomerine hold important information toward other indolizidine preparations.

The following discussion will summarize several of the strategies, focusing on the pivotal reaction step (Scheme VI). The first synthesis of monomerine (Oliver and Sonnet, 1974) provided all four possible stereoisomers of monomerine from 2,6-lutidine. The synthesis showed unambiguously that the configuration of (+)-monomerine is 3R, 5S, 8aS relating to the natural product.[86,87] Macdonald reported a stereoselective synthesis from a substituted pyrroline and 1,4-dibromopentane.[88] Stevens and Lee have employed reductive amination of a tetrahydropyridinium salt to a synthesis of (+/-)-monomerine.[89] Subsequent enantiospecific routes to monomerine have been effected using hetero Diels-Alder intermediates,[90] alkynylation of 1-acylpyridinium salts,[91] asymmetric nitrone cycloaddition,[92] and recently via a Claisen rearrangement of α-amino acids.[93] (+/-)-

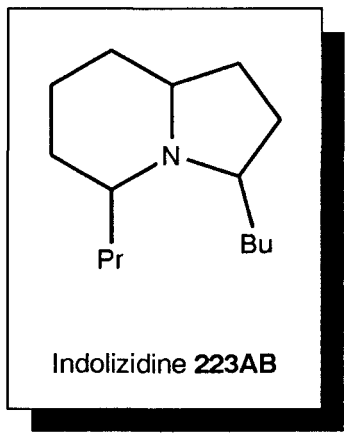
Scheme VI. Pivotal intermediates in monomerine syntheses.




Reagents: 1. TiPS-OTf / $Et_3N$; 2. LAH; 3. $(ClCO)_2$, DMSO, $Et_3N$; 4. $(EtO)_2P(O)CH_2C(O)$n-Bu, KH; 5. 10% Pd/C, $H_2$, MeOH; 6. $Ph_3PBr_2$; 7. $Et_3N$; 8. $Na_2CO_3$ / MeOH; 9. oxalic acid; 10. $NaCNBH_3$; 11. [2+2]; 12. $Et_3NHCl$; 13. HCl; 14. $NaCNBH_3$; 15. $H_2$, Pt/C, MeOH; 16. ethylene glycol, pTsOH / benzene

Monomerine has also been synthesized via a novel 2 + 2 cycloaddition of group IV metal imido complexes.[94]

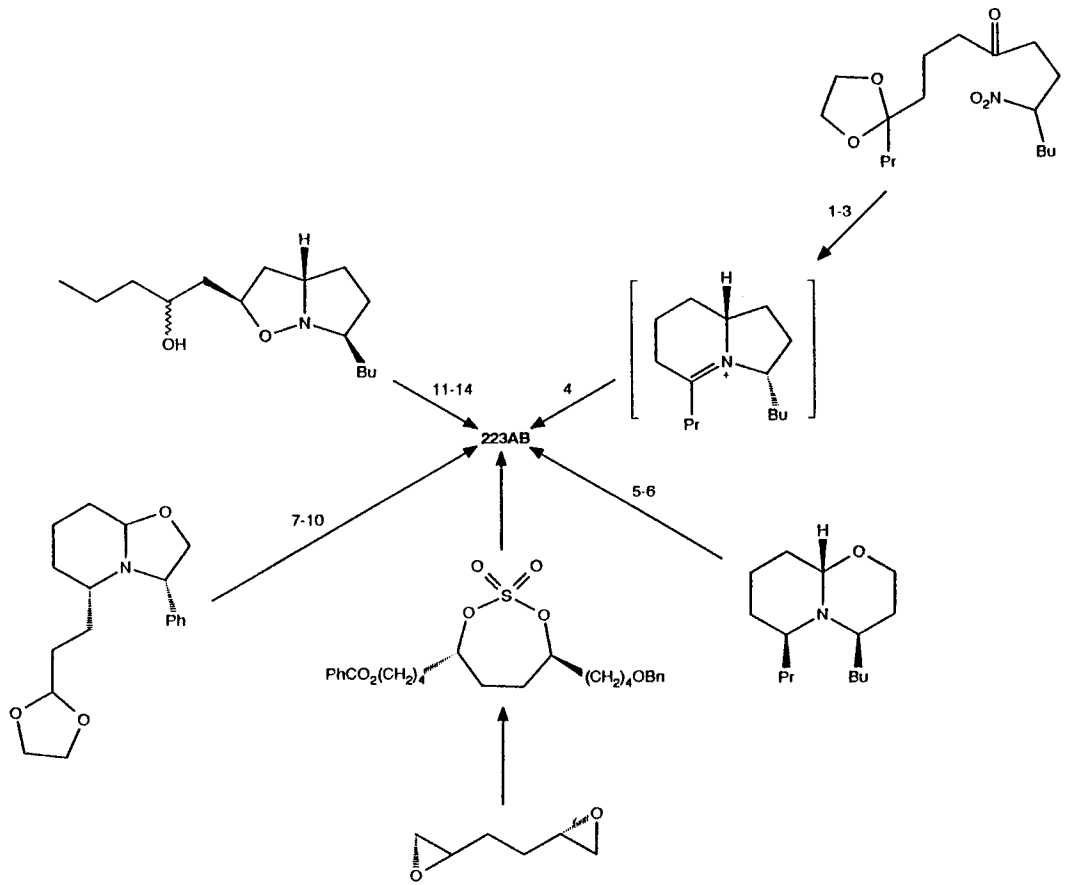
Far fewer syntheses of the 3,5-substituted indolizidine **223AB** have been accomplished, though receiving much synthetic interest. This is surprising because it differs from monomerine only in the substitution of a propyl for a methyl group (below).




Indolizidine **223AB**

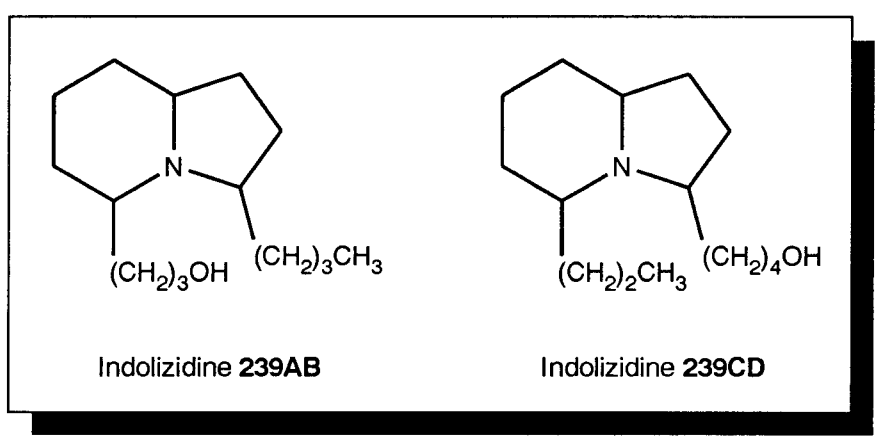
The first reported synthesis of (+/-)-**223AB** appeared in 1980 by Macdonald, and followed the synthetic strategy utilized for his monomerine synthesis.[95] Following this report, the first enantiospecific synthesis of (-)-**223AB** appeared in 1985 and was accomplished from a chiral cyano-oxazolopiperidine synthon.[96] A number of reports have utilized 1,3-dipolar cycloadditions of nitrones to synthesize indolizidine **223**. Brandi and co-workers reacted a substituted pyroline N-oxide with a hept-1-en-4-ol followed by cleavage and recyclization of the isoxazolidine to provide (+/-)-**223AB**.[97] In a later paper, reaction of N-oxides with methylenecyclopropanes followed by rearrangement of the spiro isoxazolines furnished an alternative route to this indolizidine.[98] Two stereoselective approaches to (+/-)**223AB** using Mannich condensations have also appeared in the

Scheme VII. Pivotal intermediates for the syntheses of indolizidine **223AB**.




Reagents: 1. 10% Pd/C, $H_2$, $Na_2SO_4$, MeOH; 2. oxalic acid; 3. HCl; 4. $NaCNBH_3$; 5. $(EtO)_2P(O)CN$, cat. $ZnBr_2$; 6. K, 18-crown-6; 7. PrMgBr / ether; 8. $H_2$, 10% Pd/C, MeOH; 9. $CH_2Cl_2$ - HCl, KCN; 10. BuMgBr; 11. MsCl; 12. $H_2$ 10% Pd/C; 13. NaH, $CS_2$, MeI;
14. $Bu_3SnH$, AIBN

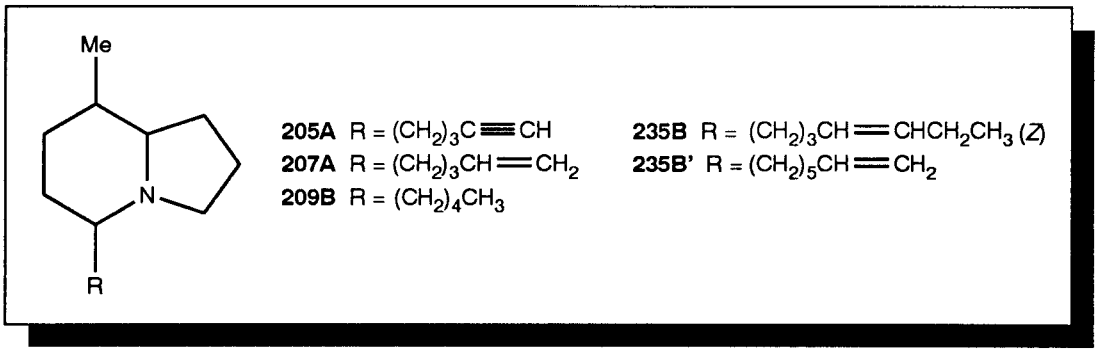
literature. Condensation of 3-amino-1-heptanol with glutaraldehyde and cyanide produces an intermediate tetrahydro-1,3-oxazine, which is then alkylated, cleaved and recyclized to **223AB**.[99] The intramolecular Mannich condensation of an acyclic precursor followed by stereoselective hydride reduction of the resulting iminium ion also has provided indolizidine **223AB**.[100] Kibayashi and co-workers[101,102] and Stevens and Lee[103] both reported syntheses of (+/-)-**223AB**, which parallel those previously reported for their synthesis of (+/-)-monomerine, using intramolecular nitroso Diels-Alder reaction, and the reductive amination of tetrahydropyridinium salts, respectively. Since 1990, only two reported syntheses of indolizidine **223AB** have appeared. The eight epimers of **223AB** have been synthesized from a common chiral synthon via cyclic sulfates by Kibayashi and Machinaga.[104] An enantioselective, ruthenium promoted synthesis of **223AB** from an amino-alcohol followed by triphenylphosphine mediated cyclization has appeared (Scheme VII).[105]




A structural isomer related to **223AB** also has been isolated that contains a hydroxyl group on the butyl chain (**239CD**). Indolizidine **239CD** also has a regioisomer

where the hydroxyl group is on the propyl chain (**239AB**) Only one synthesis of the isomeric hydroxylated indolizidine **239CD** has appeared. The chiral synthon and cyclic sulfate method used by Kibayashi in the synthesis of **223AB** was extended to provide the only synthesis of (+/-)-**239CD** to date, and confirmed the regiochemistry.[106]

The 5,8-substituted indolizidines are the most recent to be isolated from the skin of neotropical frogs.[76] All of the naturally occurring 5,8-substituted indolizidines bear a methyl group at the 8-position of the molecule. In contrast, the 5 position shows an amazing variation in both chain length and structure.

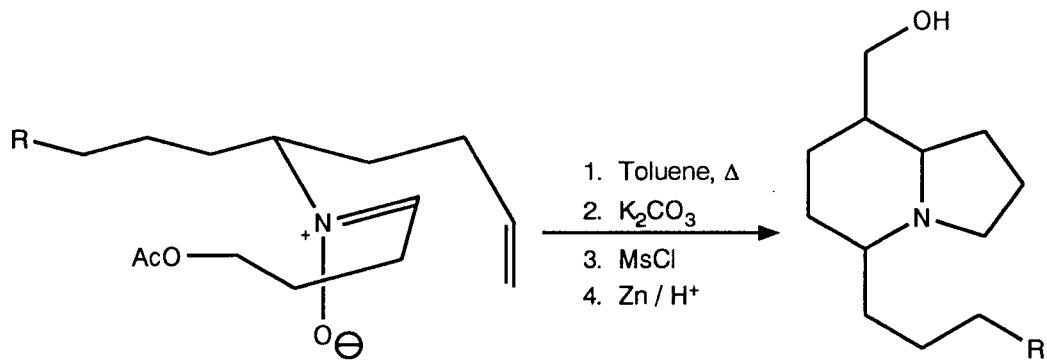



Recently three new R groups have been identified as substituents in 5,8-substituted indolizidines,[107] but no syntheses of these natural compounds have been reported to date.

**203A** R = $CH_2CH{=}CHC{\equiv}CH$ (*Z*)
**233D** R = $(CH_2)_3CH{=}CHCH{=}CH_2$ (*Z*)
**251B** R = $(CH_2)_3CH{=}CHCH(OH)CH_3$ (*Z*)

The first reported synthesis of (+/-)-**205A**, (+/-)-**207A** and an enantioselective synthesis of (-)-**209B** was accomplished in 1988 by Holmes and co-workers.[108,109] Cycloaddition of (*Z*)-alkenylnitrones (**4**) followed by reductive cleavage of the N-O bond yields (+/-)-**205A** and (+/-)-**207A**. Use of a chiral hydroxylamine in the synthesis of the (*Z*)-

alkenylnitrone provides (-)-**209B** enantioselectively. The scope of the (*Z*)-alkenylnitrone methodology has been expanded to the synthesis of racemic (+/-)-**235B**.[110]




4 5

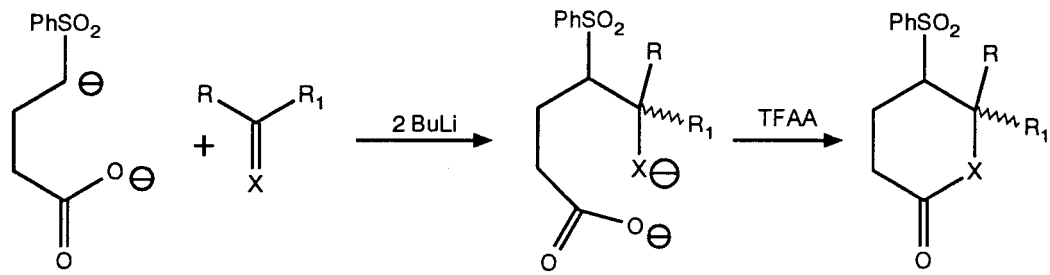
In a route analogous to their synthesis of (-)-**167B**, Polniaszek and Belmont utilized a methyl substituted chiral acyliminium ion[111] to synthesize the intermediate 8-methyl amino-nitrile, which following alkylation gave (-)-**205A** and (-)-**235A** enantioselectively.[112] A short (6 steps) asymmetric synthesis of (+)-**209B** from pyridine also has been reported.[113] In their continuing study of hetero Diels-Alder reactions for the synthesis of alkaloids, Kibayashi and Shishido have synthesized (-)-**205A**, (-)-**207A**, (-)-**209B** and (-)-**235B** via a intramolecular Diels-Alder reaction of chiral N-acylnitroso compounds.[114,115]

The synthetic approaches previously described all were directed towards a specific substitution pattern of natural indolizidines. No synthesis reported has provided entry to substitution at all three positions (3, 5 and 8) functionalized in natural indolizidnes from a common intermediate An approach that allowed functionalization at all three positions would be of great value for the synthesis of both natural and unnatural indolizidines.

Synthetic Approach - Historical

The prior sections showed that a broad range of synthetic approaches, toward indolizidines are possible but no method has used dianions. The chemistry of dianions has recently been reviewed[116] showing a broad application to the synthesis of natural products. The remote dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA)[117] has been extensively studied in our laboratory and found utility in four carbon chain extensions,[118] synthesis of substituted 6-[117] and 7-membered[119] lactones, and lactams.[120]

Specifically, condensation of the dianion of 4-PSBA (**6**, formed by reaction of 4-PSBA with 2 equivalents of BuLi at -78°C) with an aldehyde, ketone or imine (**7**) followed by anhydride-assisted cyclization provides an efficient one-pot procedure for the synthesis of lactones and lactams (**9**).

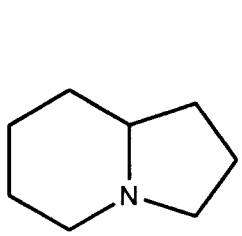



6 7 8 9

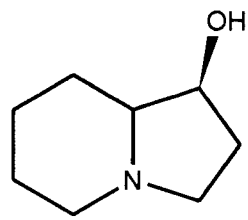
X = O or NR

The imines require prior activation with a Lewis acid ($BF_3$-$OEt_2$) before addition of the 4-PSBA. The 5-phenylsulfonyl lactams were of great interest because they could possibly serve as intermediates towards the synthesis of the large number of piperidine and piperidine-containing natural products.[121]

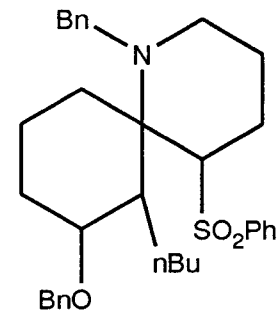
Preparation of δ-coniceine[122] and (S)-1-hydroxyindolizidine[123] via the dianion of 4-PSBA were subsequently reported. Further application of the remote dianion of 4-PSBA has provided a route to the 1-azaspiran skeleton of perhydrohistrionicotoxin.[124]




δ-Coniceine




(S)-1-Hydroxyindolizidine



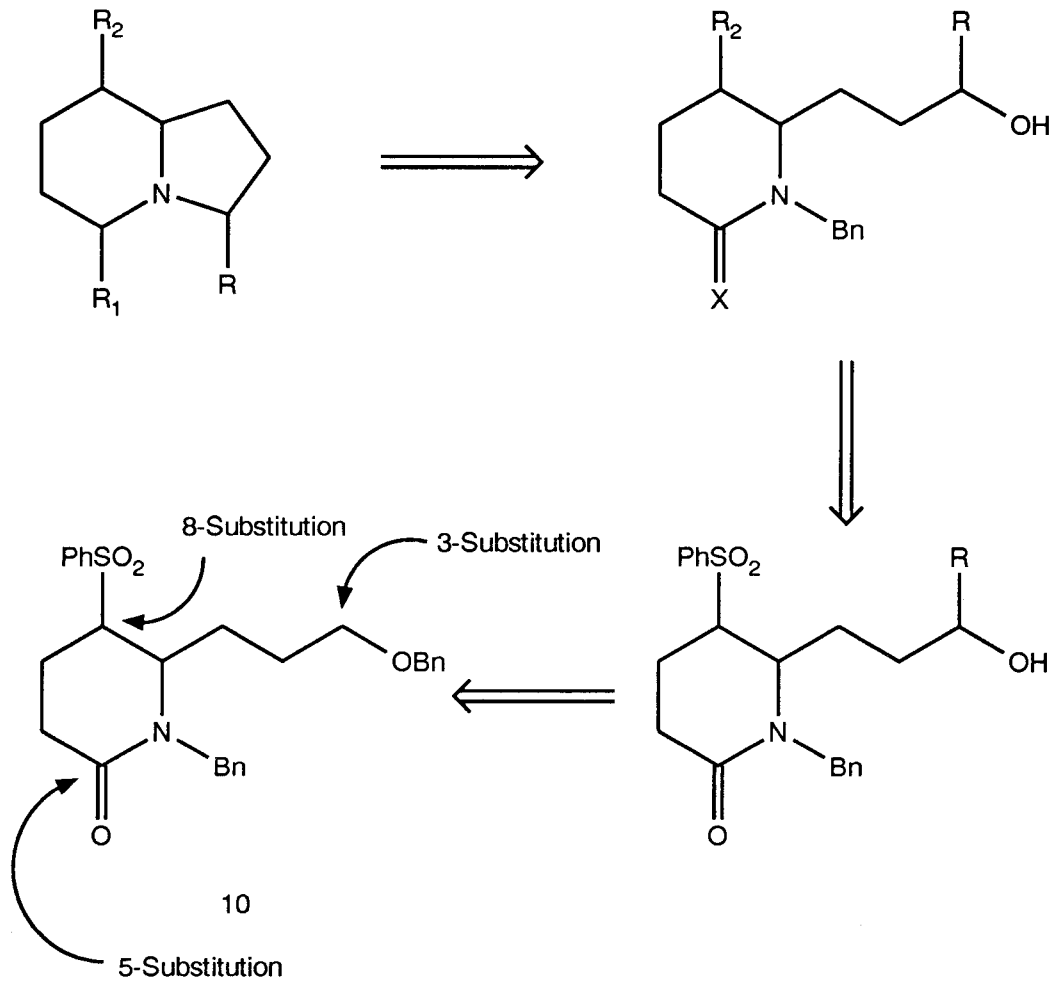

1-Azaspiran

In our continued interest in extending the usefulness of the remote dianion of 4-PSBA, we desired to develop methodology for the synthesis of alkyl substituted indolizidines. Our primary goal was to provide a simple route to a common intermediate that would furnish a wide variety of substituents at the 3-, 5- or 8-position of the indolizidine nucleus from a common intermediate.

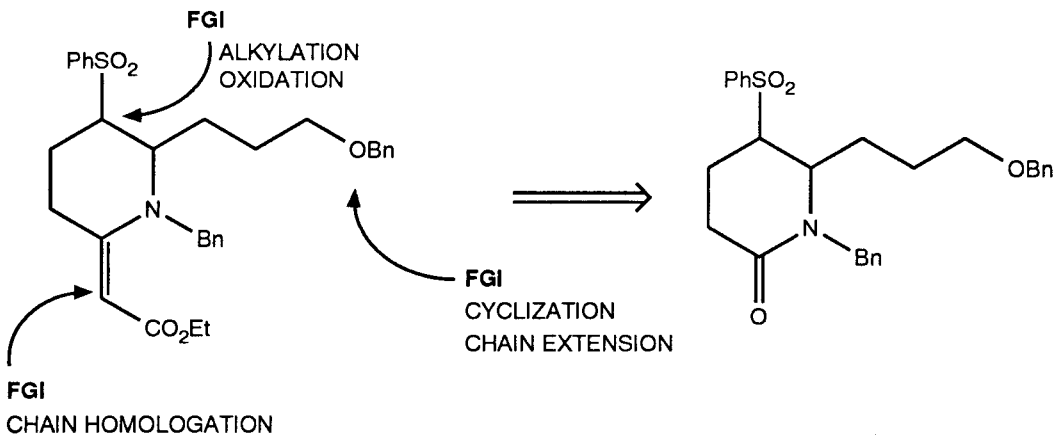
Retrosynthetically (Scheme VIII), we hypothesized that the lactam **10** used for the synthesis of δ-coniceine could provide the pivotal intermediate necessary for manipulation to any substitution pattern occurring in an indolizidine. The phenylsulfonyl provides a useful functional group for introduction of an alkyl chain at the 8 position. Reductive alkylation could be accomplished with base and the appropriate alkyl halide. Alternatively oxidative desulfonylation with bis(trimethylsilyl)peroxide[125] affords the ketone at the 8 position allowing tremendous possibilities for exploitation to the alkyl

chain required in the indolizidines. The lactam carbonyl although difficult to functionalize can be modified to a more reactive intermediate. Reaction of the lactam carbonyl with Lawesson's reagent[126] to give the thiolactam followed by reductive alkylation[127] would furnish the alkyl chain at the 5 position. The ease of these particular manipulations will also allow entry into indolizidines with more complicated alkyl substituents.

Scheme VIII.



Initial attempts proved that manipulations of the 3- and 8-position in lactam **10** were very straightforward. Functionalization of the 5-position (lactam carbonyl) proved to be extremely difficult. These results prompted the altering of the pivitol intermediate to one were 5-position substitution was more facile. Our studies showed that vinylogous carbamate **11** would provide improved access to 5-position substitution while, not altering established routes to substitution at the 3 or 8-position.




11 10

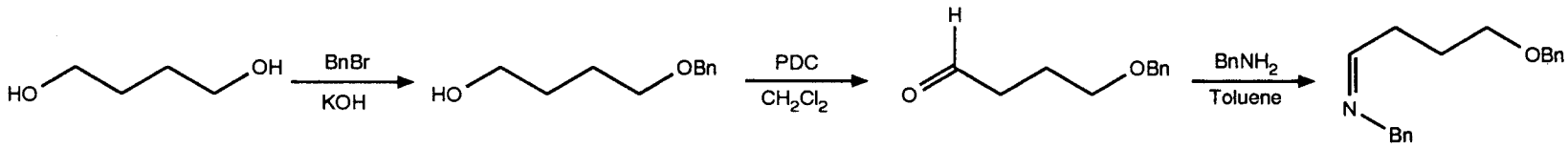
Chapter 6

# RESULTS AND DISCUSSION

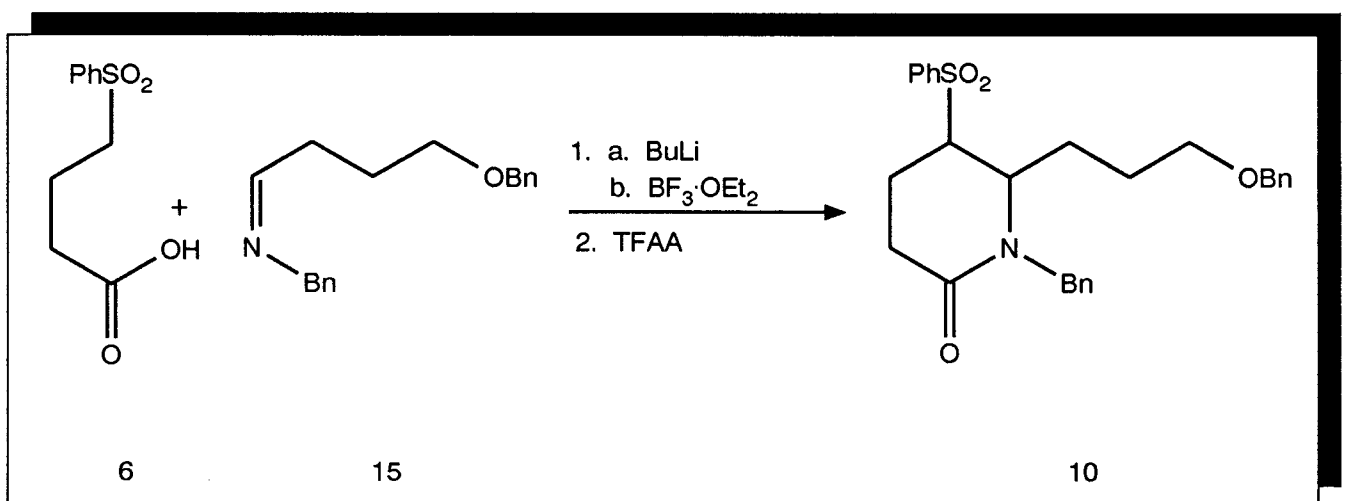
The first objective of the synthesis was to prepare the achiral lactam **10**, an intermediate used for the synthesis of δ-coniceine. 1,4-Butanediol (**12**) (Scheme IX) was protected as its monobenzyl ether (**13**) using excess diol (KOH, benzyl bromide)[128] in 91% yield based upon the benzyl bromide consumed. The yield of this reaction was increased to 99% by incremental addition of both the KOH and benzyl bromide to the diol. The monobenzyl ether (**13**) was oxidized to the aldehyde (**14**) [pyridinium chlorochromate (PCC)][129] in 67% yield. Some difficulties in isolation of the products from the black tar produced during the oxidation probably reduced the yield. It was found that by first filtering the reaction mixture through a Florisil packed funnel,[130] followed by removal of solvent and column chromatography, increased the yield to 80%. Substitution of pyridinium dichromate[131] (PDC) improved the yield to 90% in conjunction with an alternative elutant in flash chromatography. Swern oxidation[132] using dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride (TFAA) did not prove to be better than PDC, providing the aldehyde in 71% yield.

Conversion of aldehyde (**14**) to the acyclic imine (**15**) was accomplished by addition of **14** to a stirring solution of benzylamine in toluene followed by decanting the organic layer and drying over barium oxide at -4 °C for 12 hours. The imine is unstable

Scheme IX. Synthesis of achiral lactam.

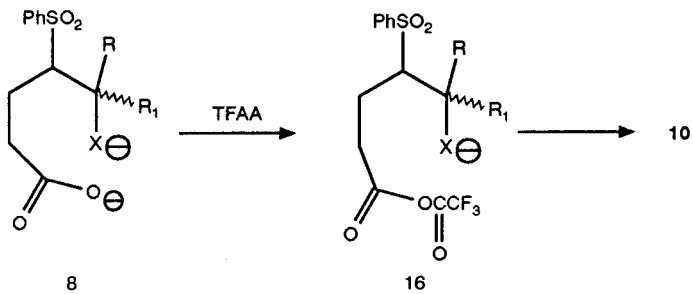



12 13 14 15




6 15 10

and used without further purification in the condensation with the dianion of 4-PSBA (**6**). The dianion of 4-PSBA is first formed by the addition of 2 equivalents of butyllithium (BuLi) in THF to provide the characteristic gold color of the dianion intermediate. In a separate flask, the imine, dissolved in THF, is activated with boron trifluoride etherate ($BF_3$-$OEt_2$) at -78 °C for 30 minutes. The activation, presumably results in the formation of a Lewis acid iminium salt which undergoes attack by a nucleophile more readily. The intermediate dianion addition product is then cyclized to the lactam by addition of TFAA.



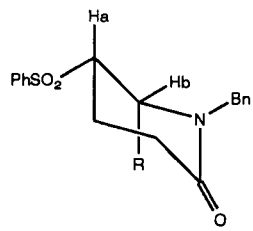

8 16

The cyclization reaction is very sensitive to the time between dianion reaction and addition of TFAA. If the reaction is allowed to continue for longer than five minutes before addition of TFAA, the reaction yields were much lower. The lower yields are probably due to rearrangement of the resulting dianion to a more stable dianion wherein the secondary anionic site is at the alpha carbon of the phenylsulfonyl as opposed to the nitrogen center. Lactam (**10**) is isolated as a mixture of fast and slow diastereomers (based on their normal phase chromatographic elution order) in 82% yield after purification.

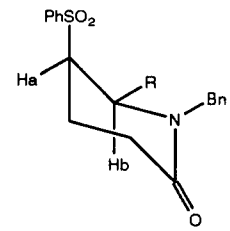
The products contain two chiral centers providing two sets of enantiomers. These products are obtained in approximately a 1:2 ratio of fast to slow diastereomer. The

predominate isomeric mixture (**10**; slow band) has been assigned the *cis* stereochemistry, which exists as conformations **17** and **18** (Figure 1), where the phenylsulfonyl and alkyl substituents are situated axial and equatorial. The other isomeric mixture (**10**; fast band) is then the *trans* configuration where the phenylsulfonyl and alkyl chains are situated diaxial (**20**), or diequatorial (**19**) in the ring.

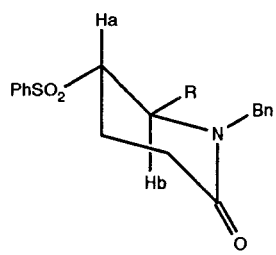
Figure 1. Chair conformation of achiral lactam.



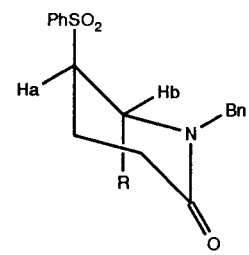

17




18




19




20

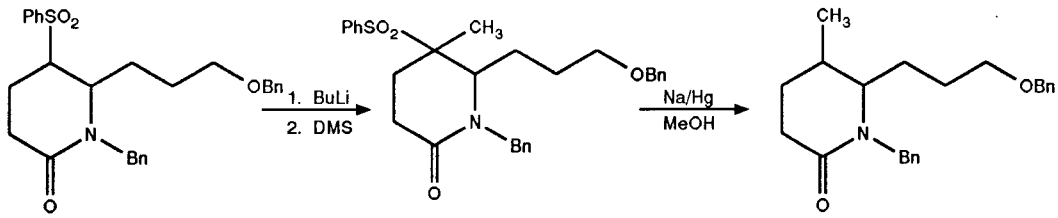
The stereochemical assignment is based on $^1$H NMR coupling constants (J) between $H_a$ and $H_b$, examination of models, and comparison to calculated J values from Karplus curves.[133] In **17** and **18**, when the two groups are *cis*, the angle θ between $H_a$ and $H_b$ is approximately 60°, and should exhibit a relatively simple $^1$H NMR spectrum with a theoretical $J_{HaHb}$ of 2.5 Hz (accounting for the electronegative phenylsulfone). In contrast, when the groups are *trans*, as is the case for **19** and **20**, two angles θ exist, giving rise

to two coupling constants, creating a more complex spectrum. As expected, $J_{HaHb}$ for the slow band was 2.6 Hz while, no single coupling constant could be identified for the fast band, although peak overlap was responsible for some of the difficulties in the assignment of the fast band.

Lactam **10** is a desirable intermediate for the synthesis of the indolizidines. The lactam contains functional groups at the projected 3-, 5- and 8-positions in the indolizidine nucleus that can be simply manipulated to other functional groups. In addition, lactam **10** can also be converted to advanced intermediates that offer unique opportunities for elaboration. This chapter presents successful approaches to natural products that can be accessed by manipulation of the 3-, 5-, and 8-position of intermediate **10**. Also, the effect of substitution at the 5-position on cyclization to the indolizidine nucleus was explored.

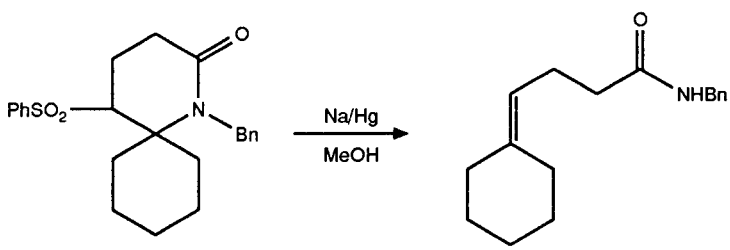
Naturally occurring indolizidines show only a methyl group at the 8-position, and therefore, we sought to find reliable methods for introduction of this group in lactam intermediate (**10**). Attempts to deprotonate fast **10** using NaH followed by alkylation with methyl iodide failed to produce the 8-substituted lactam, giving back starting material (fast **10**) as confirmed by $^1$H NMR. Sodium amide and methyl iodide or dimethyl sulfate (DMS) as the alkylating agent also gave unreacted starting material. Deprotonation with n-BuLi followed by quenching of the anion with DMS successfully produced the 8-methyl lactam (**21**) in 91% yield. It is surprising that alkylation did not occur alpha to the amide carbonyl as the relative $pK_a$'s are similar for $PhSO_2CH$ and the alpha hydrogens of an amide. The difference in reactivity may be a consequence of endocyclic (amide) verses

exocyclic (sulfone) enolate formation, the latter favored for highly substituted rings.




10 21 22

Desulfonylation of **21** to the corresponding 8-methyl compound (**22**) was accomplished using sodium amalgam in methanol. Desulfonylation was not accompanied by elimination and ring opening to give the alkene which, has been observed in previous synthesis toward azaspirans (below).[124]

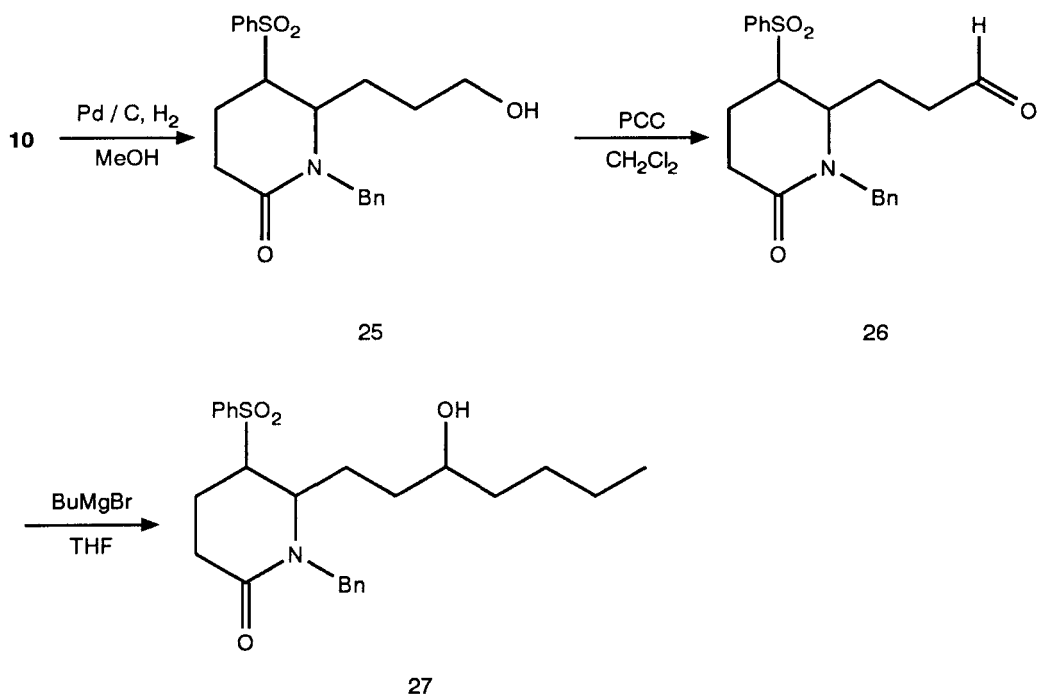



23 24

The elimination of **23** may be due in part to added ring strain imparted by the spirocyclic system. Compound **22** showed a doublet at δ 1.74 ppm ($CH_3$-, 3H) and a multiplet at δ 3.30 ppm (ring CH, 1H) in the $^1$H NMR confirming the presence of the methyl group. Two alpha carbonyl protons [-$CH_2$C(O)] remained in the $^1$H NMR indicating that alkylation did not occur at the amide enolate.

With methodology in hand for the functionalization of the 8-position, we next focused upon the introduction of substituents at the 3-position. Functionalization at the 3-position requires manipulation of the benzyl ether in lactam intermediate (**10**). This approach intended to introduce a butyl chain at the 3-position because both monomerine and indolizidine **223AB** have this common substituent at this site. Lactam **10** can be chemoselectively de-O-benzylated (10% Pd/C) under $H_2$ (< 20 psi) to furnish the alcohol (**25**) in 79% yield. Alcohol (**25**) can then be oxidized to the required aldehyde (**26**) with PCC in 76% yield (Scheme X).

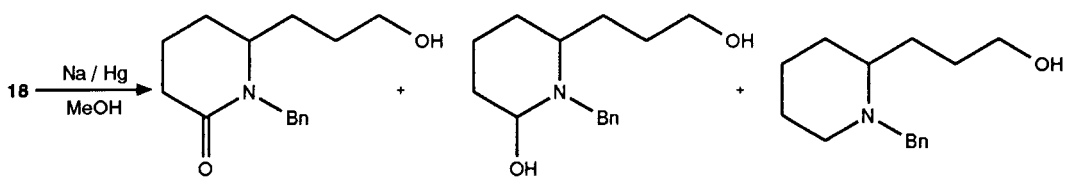
Scheme X. Introduction of 3-butyl chain.




The reaction of **26** with n-butylmagnesium bromide in dry ether (4 equivalents) proceeded poorly to the secondary alcohol (**27**). Because n-butylmagnesium bromide is unavailable

commercially and primary Grignards are somewhat sluggish to initiate, the exact concentration of the prepared solution was unknown. Following the reaction, the $^1H$ NMR of the crude reaction mixture showed a triplet at δ 9.55 ppm suggesting the presence of unreacted starting aldehyde. The secondary alcohol (**27**) was purified by flash chromatography to give a 42% yield.

It was thought that initial removal of the phenylsulfonyl group would facilitate the Grignard reaction because an extra equivalent of Grignard would not be required to remove the acidic proton alpha to the phenylsulfonyl. The phenylsulfonyl group was removed from the lactam (**25**) using sodium amalgam in methanol to give desulfonylated lactam (**28**).



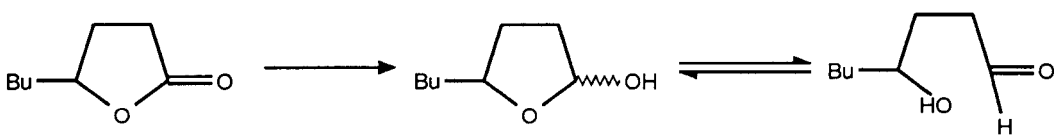

28 29 30

Desulfonylation proved to be a difficult reaction as evidenced by a $^{13}C$ NMR of the crude reaction mixture, which showed a considerable decrease in the relative height of the lactam carbonyl peak. The IR spectrum showed the presence of lactam (**28**) as well as hydroxy (**29**) and amine (**30**) functional groups, depending on the length of time the reaction was carried out. Confirmation of the lactam carbonyl reduction by sodium amalgam was made by subjecting 2-pyrrolidone to identical conditions of desulfonylation. The $^1H$ NMR and IR spectrum of the reaction mixture indicated the presence of

pyrrolidine, which was further confirmed by comparison to an authentic sample. Further, the reduction in the lactam system may not be surprising because carbohydrate lactones are reduced using sodium amalgam.[134]

The complex mixture of products was attributed to the age of the sodium amalgam. Other intermediates subjected to desulfonylations also showed an increased number of side products when the sodium amalgam used had aged. Due to the necessity of a functional group at the 5-position of the molecule to introduce functionality, an altered approach to the introduction of the butyl chain was pursued.

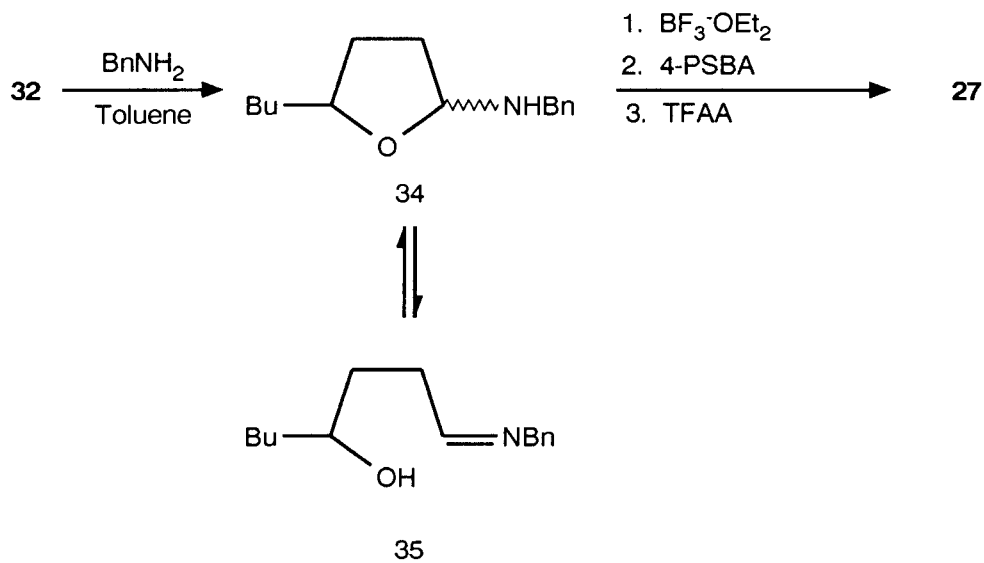
The prior synthesis of (S)-1-hydroxyindolizidine[123] showed that a functionalized side chain could be introduced into the lactam via reaction of 4-PSBA with γ-imino ethers. The imino ethers can be prepared from the corresponding lactols. In our approach, commercially available γ-octanoic lactone (**31**) was first reduced to the lactol (**32**) in 86% yield using DIBAL-H in ether at -78 °C.[135]




31 32 33

The lactol exists in equilibrium with the open chain aldehyde (**33**). Previous work showed the cyclic form predominates in common organic solvents (ether, hexane, THF, $CH_2Cl_2$). The aldehyde (**33**) would be the preferred form for conversion to the imine for subsequent condensation with the dianion of 4-PSBA in a one-pot procedure for

introduction of the 3-butyl chain. Attempts to protect the free hydroxyl group of **33** using benzyl bromide produced protected lactol and not protected alcohol. These results were not surprising as work reported on the (S)-1-hydroxyindolizidine synthesis encountered identical difficulties. As was the case with the synthesis of the (S)-1-hydroxyindolizidine, the lactol is converted to the hemi-aminal (**34**) with benzylamine and used directly in the dianion reaction with 4-PSBA.

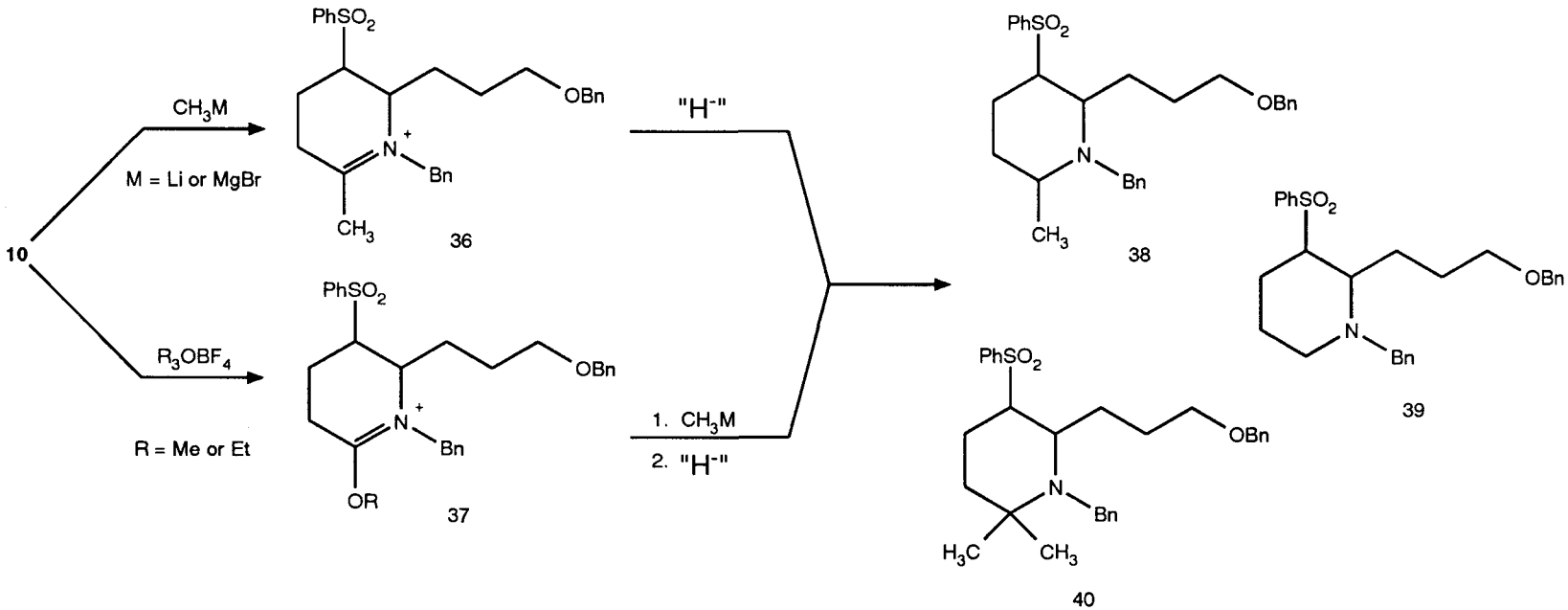



The dianion condensation reaction hinges on the existence of a small amount of the open chain imine (**35**) available at equilibrium and changing the equilibrium as the reaction proceeds. The TLC of the reaction mixture showed formation of at least eight products. This reaction complexity would be consistent with the possible formation of four diastereoisomers. In addition, the need of two equivalents of 4-PSBA in the dianion reaction further complicates the TLC. The first equivalent removes the proton on the

nitrogen of the hemi-aminal and the second effects condensation to form the lactam. The crude $^{13}C$ NMR contained four amide carbonyl peaks consistent with reaction of 4-PSBA with the hemi-aminal as well as with the imine. Purification of the reaction provided a sample that had a $^{1}H$ NMR and $^{13}C$ NMR consistent with the lactam (**27**) isolated and identified from the oxidation-Grignard route previously described (Scheme X). However, lactam **27** was isolated in only 14% yield by this method. Therefore, the use of oxidation followed by Grignard coupling is a more productive route for 3-position substitution not only based on yield but also on the versatility aldehyde **26** could provide in subsequent transformations.

With routes available to 3- and 8-substitution the functionalization of the 5-position was undertaken. Functionalization of the 5-position is critical to the versatility of the intermediate because all natural indolizidines contain a substituent at this position. The first method attempted was direct alkylation of the lactam (**10**) with methyllithium followed by reduction of the resulting iminium ion (**36**) with a hydride reagent[136] (Scheme XI). As with the Grignard reaction, an excess of base was used because the additional alpha phenylsulfonyl acidic hydrogen present in **10** consumed one equivalent of base. The reaction produced very little of the mono-methylated amine (**38**), and the mixture was found to contain mostly starting material and reduction product, piperidine (**39**). Upon exposure to air the isolated oil from the reaction, which was initially a light yellow, became bright yellow. The change in color was ascribed to oxidation of the amine to the N-oxide or hydrolysis of unreacted iminium ion.[137] Therefore attempts to further characterize this reaction were thwarted by decomposition. The alkylation of **10** was also

Scheme XI. Synthesis of 5-methyl piperidine



attempted using methylmagnesium bromide but gave similar poor results. Use of butyllithium or butylmagnesium bromide instead of methyl analogues also failed to produce products. Reactions other than attack at the lactam carbonyl were obviously taking place, in particular, the possibility of amide enolate formation was considered and shown to be a competing reaction. Evans and co-workers showed that amide enolates of lactams can be formed using lithium diisopropyl amide (LDA) and subsequently alkylated.[138] Confirmation of amide enolate formation was accomplished by reaction of **10** with 3 equivalents of BuLi and quenching the polyanion with deuterated methanol. Analysis of the $^1$H NMR showed incorporation of deuterium at the alpha position of the lactam carbonyl. Last, chromatographic separation of products from the alkylation reactions proved to be extremely difficult so alternative methods of introducing an alkyl group into position 5 were examined.

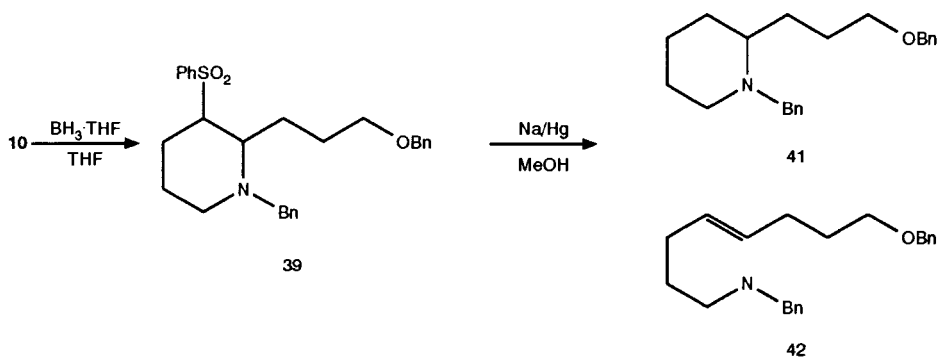
Borch[139] showed that amides and lactams could be converted to their imino ether fluoroborates and then reduced with hydride to amines. Extension of this methodology to the introduction of an alkyl group would use one equivalent of methyl anion followed by reduction with hydride. Lactam (**10**) was converted to its imino fluoroborate (**37**) (Scheme XI) in 80% yield. Compound **37** was converted to the α-methyl substituted amine (**38**) by reaction with 2 equivalents of methyllithium at -78 °C warmed to 0 °C over 1 h, and then 1 equivalent of hydride reagent added. A variety of hydride reagents were examined ($NaBH_4$, $LiAlH_4$, $NaCNBH_3$) with the best results obtained with $NaBH_4$. $^1$H NMR showed that in addition to the α-methyl amine and the reduced piperidine (**39**), it was found that a third product was formed. The third product was identified as the gem

dimethyl amine (**40**), which is formed by quenching of the initial methyl iminium ion by a second molecule of methyllithium. Once again these products were air unstable going from light yellow to bright yellow oils upon exposure to the atmosphere. The amount of oxidized product in this reaction could be reduced by using ether instead of THF as the solvent, but **38** was still isolated in less than 10% yield after chromatography.

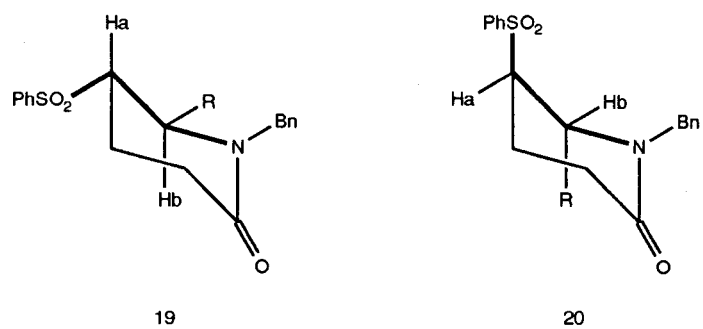
The introduction of the 5-methyl group by reductive alkylation or imino ether fluoroborate routes showed marginal promise. Both routes made use of imines to accomplish α-functionalization in amine precursors. Logically, reduction of the lactam to the piperidine and formation of an imine from the piperidine could provide a direct path to α-substitution. A large number of methods exist for the formation of imines (or iminium salts) from the corresponding amines,[140] including a recent review on the application of imminium ions to natural product synthesis.[111] The modified Polonovski reaction of amines (m-CPBA, trifluoroacetic anhydride) affords the iminium trifluoroacetates salts, which can be reacted with nucleophiles to give α-substituted amines.[141] Because of the mild conditions and compatibility with a variety of functional groups, this method was attempted to functionalize lactam **10**.

The target molecule could be synthesized by borane reduction of **10** to give piperidine **39**. Desulfonylation furnishes piperidine **41**. The reaction sequence was carried out on both diastereomers (fast and slow) of **10**. Borane reduction of the lactam (**10**) (fast or slow) gave a single product that was composed of diastereomers, resulting in corresponding fast and slow diastereomers piperidine (**39**). Desulfonylation of the fast diastereomer gave a single product while the slow diastereomer gave two products by

TLC. The two products from the desulfonylation of **10** were determined to be amine (**41**), and **42** the product of ring opening. Identification of **42** was confirmed by the appearance of olefinic carbons in the $^{13}C$ NMR and vinyl protons in the $^{1}H$ NMR. In addition, a similar ring opening was seen in the synthesis of perhydrohistrionicotoxin from our laboratory,[124] and in the desulfonylation of other synthetic intermediates in this dissertation.

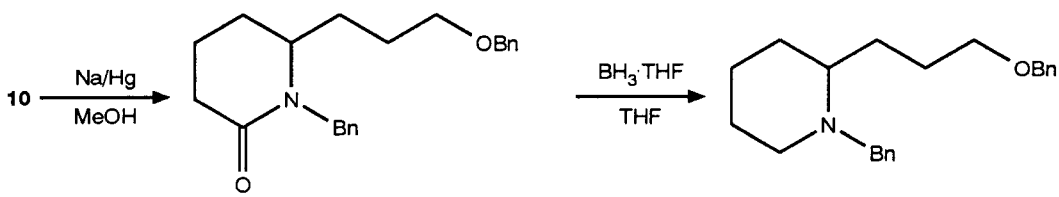



It is interesting to note that the single product from the reaction of the fast diastereomer is solely **42** while the slow diastereomer provides a 7:3 mixture of **41** and **42.** It is possible that the fast (*trans*) diastereomer is predisposed to elimination owing to an anti-periplanar orientation of the electron pair of nitrogen and the leaving phenylsulfonyl group.



Because poor yields of the desired amine (**41**) were formed by this sequence of reactions, and the electronic environment of the nitrogen in **39** would contribute to ring opening, it was decided to reverse the order of reactions. As discussed prior during the substitution at the 3-position, it was hoped that the electronic nature of the lactam compared to an amine would retard the ring opening seen in the previous desulfonylation.

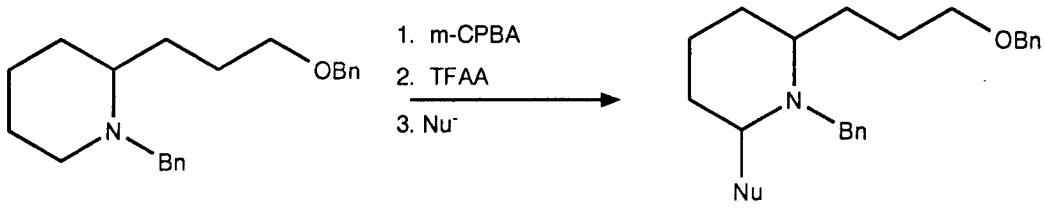
Achiral lactam (**10**), existing as a mixture of both diastereomers, was reacted with sodium amalgam in methanol to provide lactam **43** in 89% yield. The progress of the reaction could be easily monitored by TLC since loss of the phenylsulfonyl produces one spot instead of two diastereomeric spots of the achiral lactam as a result of the removal of one chiral center.




43 41

Borane reduction of **43** gives the amine (**41**) as the sole product in 95% yield.

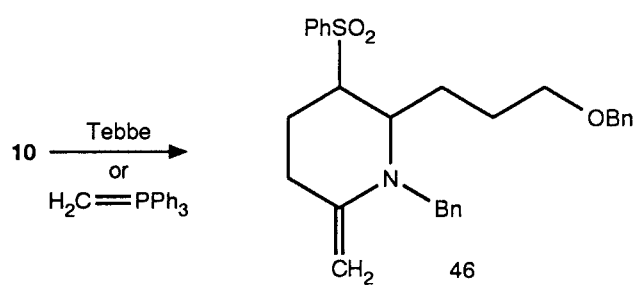
Reaction of amine **41** under the conditions of the modified Polinovski reaction provided α-substituted amines **44** and **45**, following reaction with $CN^-$ or $CH_3Li$ respectively.




41 $Nu^- = CN$ or $CH_3$ 44 Nu = CN
45 Nu = $CH_3$

Unfortunately, the use of either nucleophile in the Polonovski reaction consistently produced low yields of the respective α-substituted amines **44** (11%) and **45** (17%).

Two methods to introduce the C-5 methyl via an exocyclic methylene were also examined. Reaction of slow lactam (**10**) with Tebbe's reagent[142] failed to introduce the methylene group to afford **46**. Reaction of **10** with either the ylide derived from methyl triphenylphosphonium bromide or dimethyl methylphosphonate also did not provide the C-5 methylene compound.[143]




46

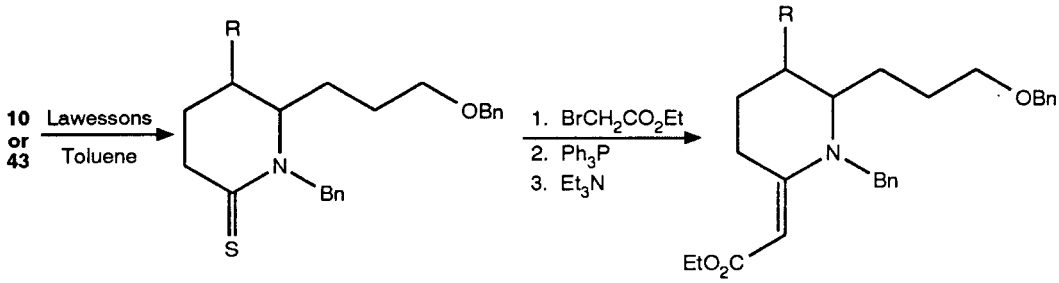
It became apparent from these aforementioned studies that introduction of the C-5 methyl group in our intermediate would be the exception and not the rule. With this in mind, it was decided (as discussed in the introduction) to alter the 5-position making it more suitable for functionalization while, not altering the 3- or 8-positions. The

vinylogous carbamate **11** was chosen for two reasons: 1. the ester offered a suitable functional group for homologation and, 2. the synthesis of the vinylogous carbamate from **10** did not require nucleophilic reagents.

The Eschenmoser reaction[144] has been used extensively for the synthesis of vinylogous carbamates from amides and lactams. The reaction enables carbon chain extensions from amide or lactam carbonyls, and proved to be valuable in the synthesis of polypyrrole alkaloids. The reaction sequences that follow were carried out on both the fast and slow diastereomers of lactam **10** [R = $PhSO_2$] and the desulfonylated lactam (**37**) [R = H] unless otherwise noted. For numbering purposes the desulfonylated lactam will be denoted by an "H" following the compounds number.

The lactam **10** is converted to the thiolactam **47** using Lawessons reagent in 96% yield (98% R = H).[126] Reaction of **47** with ethyl bromoacetate (48 hours) followed by addition of triphenylphosphine and triethylamine with stirring for an additional 24 hours gave the vinylogous carbamate (**11**) in 94% yield (91% R = H)[next page]. Unfortunately, attempts to introduce a three carbon chain via the Eschenmoser reaction, a decarboxylation sequence using a secondary bromide (ethyl 2-bromobutyrate), did not produce any vinylogous carbamate. Shiosaki has reported that secondary halides do not react in the Eschenmoser reaction because of steric crowding in the formation of the tetrasubstituted olefin.[144]

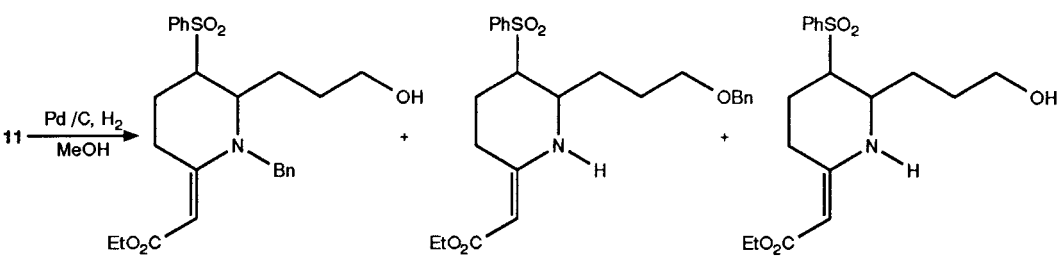
Intermediate **11**, now bearing an alternative functional group at the 5-position, was subjected to a decarboxylation method in attempts to provide the C-5 methyl group. Reaction of **11** and **11H** with a battery of hydrolyzing reagents,[143] known to decarboxylate




47 11

α,β-unsaturated esters proved to be futile.

Because the 5-position now contained an extended functional group, as opposed to a carbonyl, the cyclization to the indolizidine was explored. De-O-benzylation of slow **11** using Pd/C (<20 psi) in methanol gave back unreacted starting material. Reaction of slow **11** using Pd/C, $H_2$ (45 psi) in methanol gave products of de-O-benzylation (**48**), de-N-benzylation (**49**) and bis-debenzylation (**50**), and the corresponding saturated ester derivatives (not shown).




48 49 50

Hydrogenolysis of slow **11** using a variety of conditions also provided mixtures of products (Table V). Because no compound was formed as the major product, a more chemoselective method of de-O-benzylation was sought.

Trimethylsilyl iodide (TMS-I) is known to effect cleavage of a variety of carbon-oxygen bonds through dealkylation.[146] Specifically, TMS-I is known to cleave benzyl

TABLE V. De-O-benzylation Methods.

| Catalyst | Pressure[a] | Acid[b] | Solvent | 48 | 49 | 50 | Saturated |
|---|---|---|---|---|---|---|---|
| 10% Pd/C | B | - | MeOH | - | - | - | - |
| 10% Pd/C | B | + | MeOH | + | + | + | + |
| 10% Pd/C | P | - | MeOH | - | - | - | - |
| 10% Pd/C | P | + | MeOH | +[c] | +[c] | +[c] | +[c] |
| 10% Pd/C | P | + | EtOH | + | + | + | + |
| 5% Pd/C | B | + | MeOH | - | - | - | - |
| $Pd(OH)_2/C$ | P | - | MeOH | - | + | - | - |
| $PtO_2$ | P | - | MeOH | - | - | - | - |
| $PtO_2$ | P | + | MeOH | - | - | - | - |
| $PtO_2$ | P | + | EtOH | - | - | - | - |

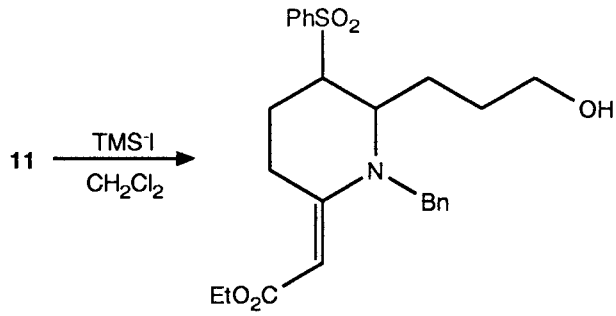
(+) = Present; (-) = Absent

[a] B = balloon pressure (< 20 psi); P = Parr shaker (45 psi)

[b] Approximately 0.20 mL of trifluoroacetic acid (TFA)

[c] Reaction also showed products of transesterification

ethers at room temperature to give the benzyl alcohol.[147] Because of this chemoselectivity, TMS-I cleavage of the benzyl ether of slow **11** was tried.



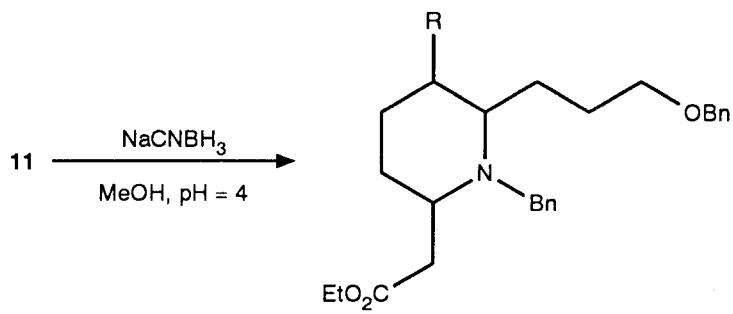

**51**

Although cleavage of esters by TMS-I is also a known transformation, it was not a concern since elevated temperatures are usually required for the transformation. This was confirmed as no ester cleavage was detected in the reaction of **51**. In addition, there was no evidence of reaction at the double bond of the vinylogous carbamate. Alcohol **51** was isolated as the sole product in 81% yield. The $^{13}C$ NMR of **51** was compared to that of the de-O-benzylated lactam (**25**), which is structurally related. An upfield shift of the carbon alpha to the oxygen and absence of the downfield peak for the methylene of the benzyl group (approximately $\delta$ 70 ppm in **10** and the vinylogous carbamate) indicated removal of the O-benzyl group. As additional evidence, a strong absorption at 3485 $cm^{-1}$ corresponding to a C-O-H stretch was observed in the IR spectrum.

Previously, cyclization to the indolizidine has been effected by initial conversion of the alcohol to the mesylate, immediate cyclization to the quaternary amine and, deprotection of the resulting N-benzyl group. Reaction of vinylogous carbamate **51** (slow) with mesyl chloride ($CH_3SO_2Cl$) showed formation of a new spot with a higher $R_f$

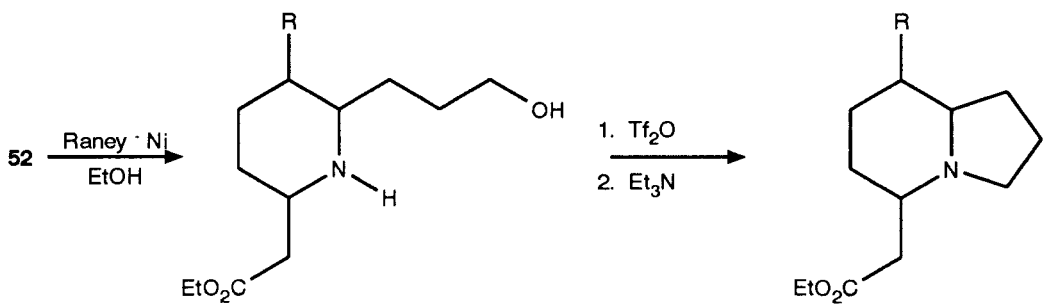
than starting material but no cyclization to the quaternary ammonium compound was evidenced (baseline in TLC). It was thought that two factors were hindering cyclization. First, the nucleophilic character of the nitrogen in the vinylogous carbamate is lower than the piperidines used in prior studies. Second, for cyclization to occur the benzyl group attached to nitrogen must adopt a conformation away from the mesyl leaving group, which is not possible in the $sp^2$ vinylogous carbamate. Because of this it was decided to reduce the double bond prior to cyclization.

Reaction of vinylogous carbamate **11** with $NaBH_4$ did not show reduction of the double bond until the pH was adjusted to approximately 4. Subsequent reactions were attempted using $NaCNBH_3$ because this reagent shows enhanced stability at lower pH. Reaction of **11** with $NaCNBH_3$ in methanol at pH = 4 gives the piperidine **52** as the sole product in 97% yield (97% R = H). At lower pH the vinylogous carbamate is protonated at nitrogen decreasing the electron density at the β-carbon of the ester, thereby allowing Michael addition by hydride. At elevated pH, the amine electron donation increases the electron density at the β-carbon of the ester and inhibits attack by a nucleophile.




52

In contrast to the reaction of **11** with TMS-I, de-O-benzylation of **52** using TMS-I failed to produce the desired alcohol. Upon addition of TMS-I to **52** a baseline spot was immediately detected by TLC, which would be consistent with ammonium salt formation. Reaction of **52** with 2 equivalents of TMS-I also failed to de-O-benzylate the material. Hydrogenolysis of **52** at both low and high pressure was attempted, but gave starting material and a complex mixture of products, respectively. Because of these results a systematic survey of de-O-benzylation reagents was undertaken. Exploratory reactions using Raney-Nickel in ethanol to our delight and surprise was found to not only effect de-O-benzylation but also de-N-benzylation as well to give **53** (R = $PhSO_2$), with no mono-de-benzylated products isolated after 24 h.




53 54

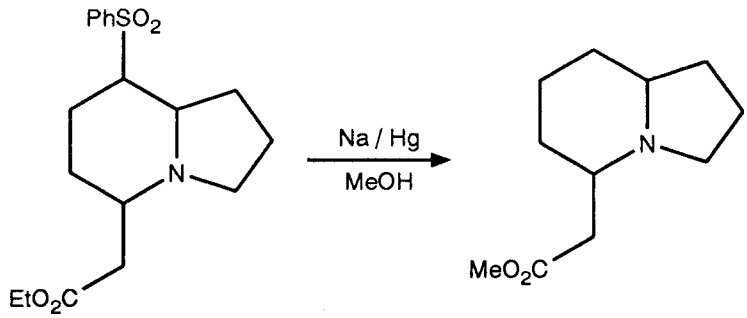
The surprising success with Raney-Nickel prompted an exploration into methods that would provide a one-pot procedure for the conversion of the vinylogous carbamate (**11**) directly into the deprotected saturated ester (**53**). The reaction required a large excess of Raney-Nickel to accomplish the reductions and showed two side products, which were

not seen when the reactions were done sequentially.

Cyclization of **53** was effected with trifluoromethanesulfonic anhydride, which following free-base with triethylamine provides the 8-phenylsulfonyl indolizidine in 70% yield. Analysis of the $^{1}H$ NMR, $^{13}C$ NMR, IR and combustion analysis confirmed the identity of the slow diastereomer of **54**. Use of IR is particularly important since 1-azabicyclo compounds give rise to absorptions called Bohlmann Bands between 2700 and 2800 $cm^{-1}$.[146] According to the Bohlmann correlation, an indolizidine will possess one or more strong infrared absorptions when two or more hydrogens attached to carbon atoms adjacent to nitrogen are oriented *trans* and diaxial to the nitrogen lone electron pair. Indolizidine **54** contains a strong absorption at 2795 $cm^{-1}$. Combustion analysis of fast **54** did not provide satisfactory results. Although $^{1}H$ NMR and $^{13}C$ NMR analysis showed loss of the ethyl group of the ester, the existence of an indolizidine was confirmed based on a Bohlmann band at 2790 $cm^{-1}$. Also interesting was the fact that deprotected piperidine **53H** did not contain an ethyl splitting pattern in the $^{1}H$ NMR. The identity of these molecules is still being investigated.

With the indolizidine nucleus complete, elaboration of the ester side chain was explored. Attempted reduction of the ester to the corresponding aldehyde with DIBAL-H failed to give satisfactory results. Reduction of the ester to the alcohol using $LiAlH_4$[149] (LAH), 2 equivalents of DIBAL-H[135] or *in situ* generation of $LiBH_4$[150] failed to reduce the ester, probably due to difficulties in control over multiple hydride additions and the presence of the phenylsulfonyl acidic hydrogens. Desulfonylation also failed to give products. This failure was again attributed to the age of the sodium amalgam used.

Preparation of fresh sodium amalgam and desulfonylation of **54** to **55** provided the 5-substituted indolizidine in 38% yield.




54 55

The isolation of indolizidine **55** as its methyl and not ethyl ester is attributed to transesterification during the sodium amalgam reaction. Methoxide is produced in large quantities in this reaction as documented in the conversion of phenylsulfone lactones to γ, δ-unsaturated methyl esters.[118] Due to the volatility of the indolizidine, (**55**) the reaction was filtered into acidic methanol to trap the indolizidine as its hydrochloride salt. It is also possible that solvent removal under reduced pressure may have caused the transesterification to occur.

# Chapter 7

# CONCLUSIONS

This investigation showed that the remote dianion-cyclization procedure can provide a versatile intermediate for the synthesis of indolizidine alkaloids. Moreover, this synthetic route has allowed entry into substitutions at the 3-, 5- and, 8-positions of the indolizidines from a common lactam intermediate. The Eschenmoser reaction to furnish the vinylogous carbamate has further extended the potential of the intermediate by providing several possible methods of chain extension for the 5-position. The study has also contributed to an understanding of structural and electronic requirements for the cyclization of the intermediates to the indolizidine nucleus.

Future research in this project should include the synthesis of indolizidines containing substitution patterns not found in the natural products, synthetic methodology for the introduction of non-alkyl functional groups and evaluation of the biological activity of these molecules.

Chapter 8

# EXPERIMENTAL

**General Methods.** $^{1}H$ and $^{13}C$ NMR were recorded on a Varian VXR-300 at 300 MHz and 75 MHz, respectively. NMR spectra were taken in deuterated chloroform ($CDCl_3$) and all chemical shifts are referenced to TMS (tetramethylsilane) as an internal standard. Infra-red spectra were run on a Perkin-Elmer 1310 spectrometer, and recorded neat (NaCl Cells) or as solutions in $CDCl_3$ with only the salient bands reported. Analytical thin layer chromatography (TLC) was conducted with aluminum backed silica plates (E. Merck). Flash chromatography was performed on Kieselgel 60, 230-400 mesh (E. Merck) using nitrogen positive pressure. Florisil (Fisher) 100-200 mesh was used where indicated. All solvents were purified by standard literature procedures.[151] Air and moisture sensitive reactions were conducted under a positive argon atmosphere utilizing standard techniques.[152] Hydrogenolyses were conducted either with double balloon pressure (<20 psi) or in a Parr shaker (45 psi). Ethyl bromoacetate (Aldrich) was distilled prior to use. Trifluoroacetic anhydride, benzylamine and triethylamine were distilled from $CaH_2$.[151] Triphenylphosphine was recrystallized from hexane[151] and 4-PSBA was recrystallized from chloroform/diethyl ether.[118] m-Chloroperbenzoic acid was stirred with phosphate buffer (pH = 7.6) for 24 h, filtered and, rinsed with ether.[151] All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI.), and used without further

purification.

**O-Benzyl 1,4-butanediol (13).**[123] 1,4-Butanediol (66 mL) was stirred in a flask at room temperature to which powdered KOH (40 g) and benzyl bromide (20 mL, 168.0 mmol) were added in four equal portions over 1 h. After 3 h stirring at room temperature, 100 mL of $H_2O$ was added and reaction extracted thrice with diethyl ether (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo.* Column chromatography (4:1, diethyl ether/petroleum ether) yielded 29.9 g of a clear oil (99%). $R_f$ = 0.33 (diethyl ether). IR 3430 $cm^{-1}$ (broad). $^1H$ NMR δ 7.35-7.26 (m, 5H), 4.52 (s, 2H), 3.64 (t, J = 5.9 Hz, 2H), 3.51 (t, J = 5.8 Hz, 2H), 2.39 (s, 1H), 1.69 (m, 4H). $^{13}C$ NMR δ 137.98, 128.29, 127.58, 127.52, 72.99, 70.29, 62.57, 30.07, 26.66.

**4-(Benzyloxy)-butan-1-al (14).**[123] 4-Benzyloxybutanol (5.0 g; 27.74 mmol) **13** was dissolved in 5.0 mL of $CH_2Cl_2$ and added to a stirred mixture of PDC (13.64 g; 36.06 mmol) in 350 mL of $CH_2Cl_2$. After 5 h, the mixture was filtered through a funnel containing Florisil and the solvent removed *in vacuo.* Column chromatography (4:1, hexane/ethyl acetate) yielded 4.45 g (90%) of a colorless oil. $R_f$ = 0.54 (diethyl ether). IR 1710 $cm^{-1}$. $^1H$ NMR δ 9.78 (t, J = 1.5 Hz, 1H), 7.35-7.25 (m, 5H), 4.49 (s, 2H), 3.51 (t, J = 6.1 Hz, 2H), 2.55 (dt, 2H, J = 1.5, 7.0 Hz), 1.95 (m, 2H). $^{13}C$ NMR δ 202.00, 128.35, 128.29, 127.79, 127.51, 72.94, 69.13, 40.99, 22.64.

**N-Benzylidene-4-(O-benzyl)-butanal (15).**[123] Aldehyde **14** (2.0 g; 11.22 mmol) was

dissolved in approximately 3 mL toluene and was added to a stirring solution of benzylamine (1.32 g; 12.34 mmol) in 2 mL toluene. The mixture turned warm and became cloudy. After stirring for 2 h at room temperature, anhydrous diethyl ether (approx. 5 mL) was added and the organic phase decanted and dried over BaO. The mixture was kept at 0 °C overnight and used without further purification in the dianion reaction. $R_f$ = 0.45 (diethyl ether). IR 1670 $cm^{-1}$. $^1H$ NMR δ 7.78 (m, 1H), 7.32-7.19 (m, 10H), 4.53 (s, 2H), 4.47 (s, 2H), 3.50 (t, J = 6.3 Hz, 2H), 2.38 (m, 2H), 1.88 (m, 2H). $^{13}C$ NMR δ 165.25, 139.10, 136.25, 128.18, 128.10, 127.64, 127.34, 127.27, 126.63, 72.71, 69.48, 64.88, 32.72, 26.11.

**1-Benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl]-2-piperidinone (10).**[123] Imine **(15)** (3.09 g; 11.55 mmol) was dissolved in 11 mL THF. The mixture was cooled to -78 °C under argon and freshly distilled boron trifluoride etherate (1.76 mL; 14.44 mmol) was added. Concurrently, the dianion of 4-PSBA was generated as follows: 4-PSBA (2.64 g; 11.55 mmol) was dissolved in 180 mL of THF, cooled to -78 °C under argon, and 18.5 mL butyllithium (1.2 M in hexane, 23.10 mmol) was added slowly. After 0.5 h, the activated imine solution was transfered to the dianion solution via cannula. The gold color of the dianion solution quenched immediately, and within 2 minutes trifluoroacetic anhydride (TFAA) (3.26 mL; 23.10 mmol) was added. The solution was allowed to warm to room temperature and 50 mL of ethyl acetate was added. The reaction mixture was extracted twice with $Na_2CO_3$ (50 mL) and a subsequent brine wash (50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash

chromatography (6:4, diethyl ether/ethyl acetate) yielded two products 4.52 g fast and slow diastereomers 82%).

**10** (Fast band): $R_f$ = 0.33 (ethyl acetate). IR 1625 $cm^{-1}$. $^1H$ NMR δ 7.68-7.08 (m, 15H), 5.49 (d, J = 14.4 Hz, 1H), 4.52 (s, 2H), 3.71 (m, 2H), 3.50 (t, J = 6.1 Hz, 2H), 3.06 (m, 2H), 2.75 (m, 1H), 2.54 (m, 2H), 2.21 (m, 1H), 2.03 (m, 1H), 1.82 (m, 2H). $^{13}C$ NMR δ 169.15, 138.18, 136.34, 133.89, 129.33, 128.70, 128.36, 128.23, 128.03, 127.70, 127.67, 127.58, 73.13, 69.94, 63.15, 54.64, 50.82, 28.54, 27.90, 27.47, 16.86.

**10** (Slow band): $R_f$ = 0.26 (ethyl acetate). IR 1635 $cm^{-1}$. $^1H$ NMR δ 7.62-7.24 (m, 15H), 5.29 (d, J = 14.7 Hz, 1H), 4.40 (s, 2H), 3.97 (d, J = 14.8 Hz, 1H), 3.68 (dt, J = 2.6, 9.7 Hz, 1H), 3.19 (m, 3H), 2.77 (m, 1H), 2.26 (m, 3H), 1.79 (m, 1H), 1.59 (m, 1H), 1.32 (m, 1H), 1.21 (m, 1H). $^{13}C$ NMR δ 169.29, 137.97, 136.81, 136.45, 133.81, 129.24, 129.18, 129.05, 128.63, 128.48, 128.34, 127.64, 127.56, 127.50, 73.03, 68.79, 60.52, 53.45, 48.03, 30.38, 28.90, 25.34, 18.73.

**1-Benzyl-5-(phenylsulfonyl)-5′-methyl-6-[3-benzyloxypropyl]-2-piperidinone (21).** Slow lactam **10** (0.313 g; 0.66 mmol) was dissolved in 4 mL of THF and cooled to -78 °C. n-BuLi (0.52 mL; 1.2 M in hexane; 0.66 mmol) was added and the reaction was stirred for 0.5 h. The -78 °C bath was removed and, dimethylsuflate (DMS) (0.07 mL; 0.66 mmol) was added and the mixture allowed to warm to room temperature. The reaction was extracted twice with $NaHCO_3$ followed by brine. The organic phase was

dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate) yielded 0.296 g of a light yellow oil (91%). $R_f$ = 0.58 (ethyl acetate). $^1H$ NMR δ 7.61-7.21 (m, 15H), 5.28 (d, J = 14.8 Hz, 2H), 4.39 (s, 2H), 3.97 (d, J = 14.8 Hz, 2H), 3.68 (d, J = 9.5 Hz, 1H), 3.22 (m, 2H), 2.28 (m, 2H), 2.04 (s, 3H), 1.77 (m, 1H), 1.57 (m, 1H), 1.25 (m, 2H). $^{13}C$ NMR δ 169.21, 137.96, 136.80, 136.12, 133.77, 129.14, 129.01, 128.58, 128.43, 128.29, 127.59, 127.51, 127.45, 72.98, 68.75, 60.49, 53.48, 53.27, 47.99, 30.34, 28.87, 25.31, 18.68.

**1-Benzyl-5-methyl-6-[3-benzyloxypropyl]-2-piperidinone (22).** Lactam **21** (0.149 g; 0.30 mmol) was dissolved in 3 mL of methanol and 6% Na/Hg was added until TLC showed consumption of starting material. After 4 h the reaction was filtered and the solvent removed. The residue was taken up in ether and extracted twice with $NaHCO_3$, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to provide **22** as a yellow oil (0.054 g, 51% yield) Anal. Calcd for $C_{23}H_{29}NO_2 \cdot H_2O$: C, 74.76; H, 7.91; N, 3.79. Found: C, 74.97; H, 8.12; N, 3.94. $R_f$ = 0.51 (diethyl ether). $^1H$ NMR δ 7.42-7.14 (m, 10H), 5.40 (d, J = 14.9 Hz, 2H), 4.49 (s, 2H), 3.92 (d, J = 14.7 Hz, 2H), 3.54 (t, 2H, J = 6.9 Hz), 3.30 (m, 1H), 2.48 (m, 2H), 1.97-1.38 (m, 8H). $^{13}C$ NMR δ 170.11, 138.19, 137.59, 128.36, 128.26, 127.64, 127.59, 127.45, 126.97, 72.97, 69.76, 55.14, 47.36, 32.00, 28.82, 26.29, 26.19, 18.07, 17.33.

**1-Benzyl-5-(phenylsulfonyl)-6-[3-hydroxypropyl]-2-piperidinone (25).**[123] Lactam **10** (1.23 g; 2.57 mmol) was dissolved in 2 mL THF and methanol was added until the

solution became cloudy (approx. 3 mL). The reaction vessel was flushed with argon, approx. 50 mg Pd/C was added followed by 0.10 mL trifluoroacetic acid. The mixture was stirred at room temperature under $H_2$ (<20 psi) overnight. Filtration and solvent removal *in vacuo* yielded 0.811 g (82%) of **25** as a clear oil of fast and slow diastereomers.

**25** (fast band): $R_f$ = 0.12 (ethyl acetate). IR 3400, 1645 $cm^{-1}$. $^1H$ NMR δ 7.70 (m, 3H), 7.55 (m, 2H), 7.35 (m, 3H), 7.21 (m, 2H), 5.44 (d, J = 14.5 Hz, 1H), 3.80 (m, 2H), 3.73 (t, J = 5.5 Hz, 2H), 3.15 (m, 1H), 2.70 (m, 1H), 2.55 (m, 2H), 2.23 (m, 1H), 2.20 (m, 1H), 1.77 (m, 4H). $^{13}C$ NMR δ 169.42, 129.40, 128.73, 128.71, 128.25, 128.21, 63.27, 62.36, 54.51, 50.75, 30.13, 28.59, 27.55, 17.08.

**25** (slow band): m.p. 135-137 °C. $R_f$ = 0.09 (ethyl acetate). IR 3400, 1635 $cm^{-1}$. $^1H$ NMR δ 7.68-7.22 (m, 10H), 5.22 (d, J = 14.6 Hz, 1H), 4.01 (d, J = 14.5 Hz, 1H), 3.67 (dt, J = 2.6, 9.7 Hz, 1H), 3.33 (m, 2H), 3.20 (dt, J = 2.4, 6.3 Hz, 1H), 2.77 (m, 1H), 2.24 (m, 3H), 1.93 (s, 3H), 1.75 (m, 1H), 1.55 (m, 1H), 1.24 (m, 1H), 1.12 (m, 1H). $^{13}C$ NMR δ 169.47, 136.55, 134.01, 129.32, 129.14, 128.74, 127.66, 61.31, 60.82, 53.31, 48.10, 30.20, 28.84, 27.77, 19.72.

**1-Benzyl-5-(phenylsulfonyl)-6-[propan-3-al]-2-piperidinone (26).** Lactam **25** (0.081 g; 0.21 mmol) was dissolved in 7 mL of $CH_2Cl_2$ and added to pyridinium chlorochromate (PCC) (0.085 g; 0.39 mmol) in 15 mL of $CH_2Cl_2$. After 4 h the reaction was filtered and

the solvent removed *in vacuo*. The residue was taken up in ether and extracted with $Na_2CO_3$ solution. The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate) yielded 60 mg (67%) as a light yellow oil. Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found C, 65.29; H, 5.93; N, 3.57. $R_f$ = 0.35 (ethyl acetate). IR 1730 $cm^{-1}$ (strong). $^1H$ NMR δ 9.55 (s, 1H), 7.60 (t, J = 5.1 Hz, 2H), 7.48 (m, 3H), 7.35 (s, 5H), 5.20 (d, J = 14.8 Hz, 2H), 4.10 (d, J = 14.7 Hz, 2H), 3.73 (m, 2H), 3.17 (m, 1H), 2.74 (m, 1H), 2.25 (m, 2H), 1.71 (m, 2H). $^{13}C$ NMR δ 199.64, 169.99, 136.40, 134.12, 129.39, 129.11, 128.75, 128.69, 128.62, 127.78, 61.18, 53.12, 48.38, 39.06, 28.96, 26.32, 20.67, 19.42.

**1-Benzyl-5-(phenylsulfonyl)-6-(3-hydroxyheptane)-2-piperidinone (27).** Magnesium turnings (0.015 g; 0.60 mmol) were suspended in 7 mL of dry ether and 1-bromobutane (0.09 g; 0.65 mmol) in 4 mL of dry ether were combined. To the resulting solution, aldehyde **26** (0.051 g; 0.13 mmol) was added in 1mL of dry ether. After 1 h the reaction was quenched with 1 mL $H_2O$, extracted twice with $CH_2Cl_2$ and the organic layer was dried over $Na_2SO_4$. The solvent was removed *in vacuo*. Column chromatography (9:1, ethyl acetate/ether) yielded 52 mg (90%) as a clear oil. Anal. Calcd for $C_{25}H_{33}NO_4S$: C, 67.69; H, 7.50; N, 3.16. Found: C, 67.91; H, 7.59; N, 3.28. $R_f$ = 0.58 (ethyl acetate). IR 3340 $cm^{-1}$ (weak), 1730 $cm^{-1}$ (strong). $^1H$ NMR δ 7.60 (t, J = 6.1 Hz, 2H), 7.43 (m, 3H), 7.33 (bs, 5H), 4.12 (m, 4H), 3.21 (m, 1H), 2.75 (m, 1H), 2.21 (m, 10H), 1.32 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H). $^{13}C$ NMR δ 170.32, 136.31, 134.03, 129.37, 129.06, 128.71, 128.63, 128.57, 127.80, 71.43, 60.41, 53.72, 48.39, 39.01, 37.26, 28.55, 22.55,

20.79, 19.31, 16.52, 14.12.

**1-Benzyl-6-[3-hydroxypropyl]-2-piperidinone (28).** Lactam **25** (0.342 g; 0.29 mmol) was dissolved in 3 mL of methanol. Na/Hg (6%) was added until TLC showed consumption of starting material but generally the reaction was stirred at room temperature for 15 h. The reaction was then filtered and the solvent removed *in vacuo* to yield 0.153 g (47%) of a colorless oil. Anal. Calcd . for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.12; N, 5.66. Found: C, 72.89; H, 8.12; N, 5.02. $R_f$ = 0.11 (ethyl acetate). IR 3445 $cm^{-1}$. $^1H$ NMR δ 7.33-7.20 (m, 5H), 5.38 (d, J = 15.1 Hz, 2H), 4.25 (m, 1H), 3.92 (m, 1H), 3.60 (t, J = 5.6 Hz, 2H), 3.29 (m, 1H), 2.50 (t, J = 6.1 Hz, 2H), 1.92-1.37 (m, 7H). $^{13}C$ NMR δ 170.52, 137.11, 128.54, 128.45, 127.59, 127.52, 127.17, 62.04, 55.11, 47.48, 31.39, 28.72, 28.08, 25.90, 16.79.

**1-Benzyl-6-[3-hydroxypropyl]-piperidine (30).** Piperidine **30** was isolated as a less polar side product in the synthesis of **28**. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.57; H, 9.68; N, 5.92. $R_f$ = 0.05 (ethyl acetate). IR 3450$cm^{-1}$. $^1H$ NMR δ 7.34-7.20 (m, 5H), 5.38 (d, J = 15.1 Hz, 2H), 4.61 (bs, 1H), 3.96 (m, 1H), 3.59 (t, J = 6.4 Hz, 2H), 3.32 (m, 1H), 2.51 (t, J = 5.6 Hz, 2H), 1.91-1.40 (m, 9H). $^{13}C$ NMR δ 137.15, 128.65, 128.56, 127.68, 127.62, 127.29, 62.04, 55.26, 47.62, 31.43, 28.77, 28.22, 28.14, 25.97, 16.84.

**γ-Octanoic lactol (32).** γ-Octanoic lactone (2.0 g; 14.06 mmol) in 100 mL of ether at -78

°C was reacted with DIBAL-H (28 mL; 0.5 M in hexane). The reaction was stirred at -78 °C for 4 h and allowed to warm to room temperature overnight. An equal volume of a 1% NaOH solution was added and stirred for 10 min. The aqueous layer was extracted thrice with ether, dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (1:1, diethyl ether/petroleum ether) yielded 0.487 g of a clear oil (25%). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.19. Found: C, 66.59; H, 11.16. $R_f$ = 0.23 (1:1, diethyl ether/petroleum ether). IR 3425 $cm^{-1}$ (strong). $^1H$ NMR δ 4.47 (m, 2H), 2.51 (m, 2H), 2.32 (m, 1H), 1.94 (m, 2H), 1.63 (m, 2H), 1.38 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H). $^{13}C$ NMR δ 177.21, 80.98, 35.21, 28.80, 27.95, 27.28, 22.37, 13.85.

**N-Benzyl-2-amino-5-butyl-tetrahydrofuran (34).** Lactol **32** (0.037 g; 0.26 mmol) was dissolved in 1 mL of toluene and added to a stirring solution of benzylamine (0.031 g; 0.27 mmol) in 1.5 mL of toluene. The reaction was stirred at room temperature for 48 h. At this time, the solvent was removed *in vacuo* and the benzyl amine removed by further warming to 50 °C to yield 52.9 mg (87%), of product. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.86; H, 9.68; N, 5.64. $R_f$ = 0.64 (ethyl acetate). IR 3385 $cm^{-1}$ (strong), 1660 $cm^{-1}$ (weak), 1595 $cm^{-1}$ (strong). $^1H$ NMR δ 7.44-7.18 (m, 5H), 4.87 (t, J = 6.8 Hz, 1H), 4.72 (t, J = 6.8 Hz, 1H), 4.05 (m, 2H), 3.89 (m, 4H), 2.20 (m, 1H), 2.01 (m, 1H), 1.77-1.22 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H). $^{13}C$ NMR δ 128.55, 128.32, 128.19, 126.82, 126.74, 78.41, 49.79, 36.58, 32.71, 31.85, 30.29, 28.39, 22.82, 14.07.

**1-Benzyl-6-(3-benzyloxypropyl)-2-ethoxy-5-(phenylsulfonyl)piperidinium tetrafluoroborate (37).** Triethyloxonium tetrafluoroborate (0.123 g; 0.83 mmol) was added to a stirring solution of lactam **10** (0.26 g; 0.54 mmol) in 5mL $CH_2Cl_2$. The reaction was stirred for 24 h and then the solvent was removed *in vacuo* to yield 293 mg of product (87%). $R_f$ = 0.50. IR 3420 $cm^{-1}$ (weak) 1110 $cm^{-1}$ (strong) 1000 $cm^{-1}$ (strong). $^1H$ NMR 7.67 (t, J = 5.2 Hz, 2H), 7.40 (m, 3H), 7.31 (m, 10H), 4.38 (m, 4H), 3.99 (t, 2H, J = 6.8 Hz), 3.38 (m, 4H), 3.11 (m, 1H), 2.60 (m, 1H), 2.21 (m, 2H), 1.98 (m, 1H), 1.45 (m, 1H), 1.27 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H). $^{13}C$ NMR 176.75, 136.82, 135.34, 134.70, 131.27, 129.94, 129.85, 129.68, 129.61, 129.24, 129.13, 129.06, 128.52, 128.41, 128.36, 128.13, 128.08, 72.99, 68.45, 60.13, 56.35, 56.25, 52.21, 48.69, 38.43, 27.82, 25.08, 22.54.

**1-Benzyl-2-[3-benzyloxypropyl]-3-(phenylsulfonyl)piperidine (39).** Lactam **10** (1.56 g; 3.27 mmol) was dissolved in 7 mL of THF and cooled to 0 °C in an ice bath. $BH_3$-THF (10 mL; 1.0 M in THF) was slowly added and stirred for 1.5 h. The reaction was allowed to warm to room temperature and the excess borane was hydrolyzed with 10% NaOH (careful addition is necessary as the reaction is very vigorous). Partitioning between ethyl acetate and $Na_2CO_3$ followed by drying the organic layer over $MgSO_4$ and solvent removal *in vacuo* yields **39** (1.32 g, 87%) as the sole product. Anal. Calcd for $C_{28}H_{33}NO_3S$: C, 72.53; H, 7.17; N, 3.02. Found: C, 72.48; H, 7.21; N, 2.98.

**39** (fast band): $R_f$ = 0.59 (ethyl acetate). $^1H$ NMR δ 7.89 (d, J = 2.8 Hz, 2H),

7.64 (t, J = 2.9 Hz, 1H), 7.55 (t, J = 2.9 Hz, 2H), 7.30 (m, 10H), 4.50 (m, 2H), 3.72 (q, 2H J = 12.8 Hz), 3.45 (m, 4H), 3.28 (m, 1H), 2.49 (m, 2H), 2.10-1.20 (m, 7H). $^{13}$C NMR δ 139.12, 133.34, 129.24, 129.04, 129.01, 128.74, 128.61, 128.24, 128.17, 127.60, 127.53, 127.42, 127.34, 126.98, 72.89, 70.41, 61.46, 56.91, 42.53, 30.39, 27.33, 22.11, 20.86, 20.36.

**39** (slow band): $R_f$ = 0.55 (ethyl acetate). $^1$H NMR δ 7.84 (d, J = 3.1 Hz, 2H), 7.58 (t, J = 3.0 Hz, 1H), 7.46 (t, J = 3.0 Hz, 2H), 7.30 (m, 10H), 4.44 (s, 2H), 3.67 (m, 2H), 3.38 (m, 4H), 3.08 (m, 1H), 2.47 (m, 2H), 2.14-1.30 (m, 7H). $^{13}$C NMR δ 139.01, 138.17, 132.96, 128.72, 128.40, 128.34, 128.05, 127.91, 127.29, 127.23, 126.54, 72.68, 69.53, 60.13, 56.83, 45.14, 26.49, 22.07, 20.89, 20.59, 20.31.

**1-Benzyl-6-[3-benzyloxypropyl]piperidine (41).** Piperidine **39** (1.25 g; 2.71 mmol) was dissolved in 10 mL of methanol and 6% Na/Hg was added in excess. The reaction was stirred at room temperature for 16 h. The reaction mixture was filtered and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate) yielded two products 0.62 g of **41** (77% yield) and 0.18 g of **42** (20% yield). Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.23; N, 4.33. Found: C, 81.85; H, 9.23; N, 4.40. (less polar) $R_f$ = 0.12 (ethyl acetate). $^1$H NMR δ 7.30 (m, 10H), 4.50 (s, 2H), 3.98 (d, J = 5.2 Hz, 1H), 3.48 (m, 2H), 3.22 (d, J = 5.1 Hz, 1H), 2.76 (m, 1H), 2.31 (m, 1H), 2.04 (m, 1H), 1.71 (m, 6H), 1.46 (m, 3H), 1.30 (m, 1H). $^{13}$C NMR δ 138.56, 128.77, 128.22, 127.98, 127.48, 127.35, 126.48, 72.81, 70.76, 60.41, 57.57, 51.66, 30.22, 28.21, 25.66, 25.19, 23.73.

**1-Benzyl-8-benzyloxy-oct-4-ene (42).** Polar product from reaction of **39** with 6% Na/Hg. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.57; H, 8.96; N, 4.40. $R_f$ = 0.33 (ethyl acetate). $^1H$ NMR δ 7.38 (m, 10H), 5.51 (m, 2H), 4.59 (s 2H), 3.87 (s, 2H), 3.56 (m, 3H), 2.72 (t, J = 7.0 Hz, 2H), 2.16 (m, 3H), 1.78 (m, 2H), 1.67 (m, 2H), 1.31 (m,1H). $^{13}C$ NMR δ 140.33, 138.47, 130.10, 129.75, 128.15, 128.13, 127.89, 127.39, 127.26, 126.65, 72.74, 69.62, 53.98, 48.83, 30.30, 29.83, 29.57, 29.09.

**1-Benzyl-6-[3-benzyloxypropyl]-2-piperidinone (43).** A mixture of both diastereomers of **10** (2.17 g; 4.55 mmol) were dissolved in 16 mL of methanol and an excess 6% Na/Hg was added. After 3 h the reaction was filtered and the solvent removed *in vacuo.* Flash chromatography (9:1 ethyl acetate/diethyl ether) yields 1.53 g (89%) of a colorless oil. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.28; H, 8.13; N, 4.19. $R_f$ = 0.32 (ethyl acetate). $^1H$ NMR δ 7.28 (m, 10H), 5.38 (d, J = 14.9 Hz, 2H), 4.48 (s, 2H), 3.92 (d, J = 15.1 Hz, 2H), 3.42 (t, J = 6.2 Hz, 2H), 3.28 (m, 1H), 2.48 (m, 2H), 1.98-1.23 (m, 6H). $^{13}C$ NMR δ 170.13, 138.23, 137.63, 128.40, 128.29, 127.63, 127.51, 127.48, 127.01, 73.00, 69.79, 55.17, 47.39, 32.04, 28.85, 26.33, 26.22, 17.37.

**1-Benzyl-5-methyl-6-[3-benzyloxypropyl]piperidine (44).** Piperidine (**41**) (0.055 g; 0.17 mmol) was dissolved in 3 mL $CH_2Cl_2$ and cooled to -15 °C in an ice salt bath. m-CPBA (0.059 g; 0.34 mmol) in 5 mL of $CH_2Cl_2$ was added slowly and stirred for 0.5 h. The ice bath was removed and the reaction cooled to -78 °C and TFAA (0.082 g; 0.39 mmol) was added and the reaction stirred an additional 0.5 h. Methyllithium (0.2 mL; 1.0 M in

hexane) was carefully added and the reaction allowed to warm to room temperature. Partitioning between ethyl acetate and $Na_2CO_3$, drying of the organic layer over $MgSO_4$ and solvent removal *in vacuo* provides the crude product. Flash chromatography (6:4, diethyl ether/petroleum ether) yields 0.006 g (11%) as a yellow oil. $R_f$ = 0.36 (diethyl ether). $^1H$ NMR δ 7.31 (m, 10H), 4.53 (s, 2H), 4.00 (d, J = 15.5 Hz, 1H), 3.50 (m, 1H), 3.20 (d, J = 15.6 Hz, 1H), 2.80 (m, 1H), 2.32 (m, 1H), 2.05 (m, 1H), 1.65 (m, 6H), 1.46 (m, 3H), 1.32 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H).

**1-Benzyl-5-cyano-6-[3-benzyloxypropyl]piperidine (45).** Piperidine **41** (0.171 g; 0.53 mmol) was dissolved in 3 mL $CH_2Cl_2$ and cooled to -15 °C in an ice salt bath. m-CPBA (0.184 g; 1.07 mmol) in 5 mL of $CH_2Cl_2$ was added slowly and the reaction stirred for 0.5 h. The ice bath was removed, TFAA (0.225 g; 1.07 mmol) was added and the reaction stirred an additional 0.5 h. KCN (0.070 g; 1.07 mmol) in 5 mL of $H_2O$ was added and the reaction allowed to warm to room temperature. Partitioning between ethyl acetate and saturated $Na_2CO_3$, drying of the organic layer over $MgSO_4$, and solvent removal *in vacuo* provided the crude product. Flash chromatography (6:4, diethyl ether/petroleum ether) yielded **45** (0.030 g, 17%) as a yellow oil. $R_f$ = 0.70 (diethyl ether). $^1H$ NMR δ 7.30 (m, 10H), 4.51 (s, 2H), 3.96 (d, J = 15.9 Hz, 1H), 3.61 (m, 1H), 3.23 (d, J = 16.1 Hz, 1H), 3.05 (m, 1H), 2.33 (m, 1H), 2.08 (m, 1H), 1.70 (m, 6H), 1.42 (m, 3H), 1.28 (m, 1H).

**1-Benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl]piperidin-2-thione (47).** Lawesson's

reagent (1.30 g; 3.22 mmol) was added to lactam **10** (3.08 g; 6.45 mmol) in 12 mL of toluene and refluxed for 4 h. The solvent was removed *in vacuo*, and the mixture flash chromatographed (95:5, methylene chloride/ethyl acetate) to yield 3.05 g (96%) of the thiolactam **47** as a gold oil. Anal. Calcd for $C_{28}H_{31}NO_3S_2 \cdot 1/2\ H_2O$: C, 66.89; H, 6.41; N, 2.78. Found: C, 66.80; H, 6.34; N, 2.78.

**47** (fast band): $R_f$ = 0.32 (ethyl acetate). $^1$H NMR δ 7.64 (m, 3H), 7.46 (t, J = 5.7 Hz, 2H), 7.28 (m, 10H), 6.53 (d, J = 14.3 Hz, 1H), 4.52 (s, 2H), 4.10 (d, J = 14.3 Hz, 1H), 4.01 (m, 1H), 3.50 (t, J = 6.1 Hz, 2H), 3.39 (m, 1H), 3.19 (m, 1H), 3.00 (m, 1H), 2.34 (m 1H), 2.22 (m 1H), 1.93 (m, 2H), 1.78 (m, 2H). $^{13}$C NMR δ 199.63, 138.05, 137.78, 134.62, 133.92, 129.34, 128.77, 128.34, 128.24, 128.13, 127.84, 127.67, 127.59, 73.15, 69.69, 62.85, 58.02, 57.42, 38.53, 27.39, 26.70, 17.34.

**47** (slow band): $R_f$ = 0.29 (ethyl acetate). $^1$H NMR δ 7.60 (m, 3H), 7.47 (t, J = 4.2 Hz, 2H), 7.32 (m, 10H), 5.86 (d, J = 14.4 Hz, 1H), 4.77 (d, J = 14.7 Hz, 1H), 4.41 (s, 2H), 4.04 (m, 1H), 3.31 (m, 4H), 2.81 (m, 1H), 2.03 (m, 2H), 1.72 (m, 1H), 1.67 (m, 1H), 1.41 (m, 1H), 1.26 (m, 1H). $^{13}$C NMR δ 201.08, 137.95, 136.61, 134.87, 134.05, 129.31, 128.98, 128.72, 128.66, 128.37, 127.68, 127.54, 73.08, 68.72, 61.91, 56.13, 55.95, 39.23, 31.58, 25.26, 20.13.

**1-Benzyl-6-[3-benzyloxypropyl]piperidin-2-thione (47H).** Lawesson's reagent (0.998 g; 2.47 mmol) was added to lactam **10** (1.66 g; 4.93 mmol) in 8 mL of toluene and

refluxed for 4 h. The solvent was removed *in vacuo*, and the mixture flash chromatographed (48:2:50, methylene chloride/acetonitrile/hexane) to yield 1.70 g (98%) of the thiolactam **47H** as a gold oil. Anal. Calcd for $C_{22}H_{27}NOS$: C, 74.74; H, 7.70; N, 3.96. Found: C, 74.78; H, 7.90; N, 3.94. $R_f$ = 0.38 (ethyl acetate). $^1H$ NMR δ 7.31 (m 10H), 6.47 (d, J = 14.9 Hz, 1H), 4.48 (s 2H), 4.32 (d, J = 14.9 Hz, 1H), 3.47 (m 4H), 3.15 (t, J = 5.8 Hz, 2H), 1.85 (m 2H), 1.72 (m, 4H), 1.66 (m, 1H). $^{13}C$ NMR δ 200.96, 138.10, 135.61, 128.60, 128.34, 127.59, 127.51, 127.49, 73.10, 69.47, 58.07, 55.37, 41.14, 28.70, 26.47, 25.84, 17.05.

**1-Benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methylidene] piperidine (11).** Thiolactam **47** (2.77 g; 5.61 mmol) in 7 mL dry acetonitrile was stirred at room temperature with ethyl bromoacetate (1.17 g; 7.01 mmol) for 48 h. The reaction was then diluted with 24 mL of $CH_2Cl_2$ and after 10 minutes, triphenylphosphine (3.31 g; 12.62 mmol) was added and stirred an additional 0.5 h. Triethylamine (1.70 g; 16.83 mmol) was then added and the reaction stirred for an additional 24 h. The mixture was diluted with ethyl acetate (30 mL), washed with saturated $Na_2CO_3$, brine, and dried over $MgSO_4$. Flash chromatography (9:1, methylene chloride/ethyl acetate) yielded 2.89 g (94%) of **11** as a gold oil. Anal. Calcd for $C_{32}H_{37}NO_5S \cdot 1/2\ H_2O$: C, 69.04; H, 6.88; N, 2.52. Found: C, 69.09; H, 6.75; N, 2.49.

**11** (fast band): $R_f$ = 0.45 (diethyl ether). IR 1755 $cm^{-1}$. $^1H$ NMR δ 7.77 (d, J = 5.4 Hz, 2H), 7.63 (t, J = 5.4 Hz, 1H), 7.50 (t, J = 2.3 Hz, 2H), 7.28 (m, 10H), 4.72 (s,

2H), 4.43 (m, 3H), 4.22 (m, 2H), 4.01 (m, 2H), 3.87 (m, 1H), 3.71 (m, 1H), 3.33 (m, 4H), 2.23 (m, 1H), 1.92 (m, 1H), 1.68 (m, 2H), 1.45 (m, 1H), 1.22 (m, 3H). $^{13}$C NMR δ 168.46, 160.96, 135.78, 133.90, 129.21, 128.85, 128.57, 128.30, 127.52, 127.35, 88.09, 73.02, 69.30, 63.77, 58.60, 55.92, 55.13, 33.26, 25.47, 23.36, 20.34, 14.62.

**11** (slow band): $R_f$ = 0.42 (diethyl ether). IR 1750 cm$^{-1}$. $^1$H NMR δ 7.75 (d, J = 5.1 Hz, 2H), 7.64 (t, J = 5.4 Hz, 1H), 7.52 (t, J = 2.1 Hz, 2H), 7.26 (m, 10H), 4.69 (s, 1H), 4.43 (m, 3H), 4.20 (m, 2H), 4.01 (m, 2H), 3.86 (m, 1H), 3.34 (m, 4H), 2.23 (m, 1H), 1.95 (m, 1H), 1.56 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H). $^{13}$C NMR δ 168.28, 160.80, 138.02, 136.69, 135.68, 133.79, 129.09, 128.69, 128.16, 127.37, 127.35, 127.20, 87.94, 72.84, 69.15, 63.55, 58.43, 55.86, 54.98, 33.09, 25.31, 23.20, 20.16, 14.50.

**1-Benzyl-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methylidene]piperidine (11H).** Thiolactam **47H** (1.45 g; 4.11 mmol) in 7 mL dry acetonitrile was stirred at room temperature with ethyl bromoacetate (0.859 g; 5.14 mmol) for 48 h. The reaction was then diluted with 22 mL of $CH_2Cl_2$ and after 10 minutes, triphenylphosphine (1.62 g; 6.17 mmol) was added and stirred an additional 0.5 h. Triethylamine (1.25 g; 12.33 mmol) was then added and the reaction stirred for an additional 24 h. The mixture was diluted with ethyl acetate (30 mL), washed with saturated $Na_2CO_3$, brine and dried over $MgSO_4$. Flash chromatography (95:5, methylene chloride/ethyl acetate) yielded 1.52 g (91%) of **11H** as a gold oil. Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.81; H, 7.94; N, 3.31. $R_f$ = 0.55 (diethyl ether). IR 1750 cm$^{-1}$. $^1$H NMR δ 7.29 (m,

8H), 7.13 (d, J = 6.8 Hz, 2H), 4.51 (m, 4H), 4.27 (d, J = 16.9 Hz, 1H), 4.40 (m, 2H), 3.41 (t, J = 6.1 Hz, 2H), 3.26 (m, 2H), 3.13 (m, 2H), 1.70 (m, 6H), 1.47 (m, 1H), 1.17 (t, 3H, J = 7.1 Hz). $^{13}C$ NMR δ 168.83, 162.10, 138.21, 136.50, 128.49, 128.26, 127.47, 126.90, 126.39, 84.22, 72.97, 68.80, 58.23, 58.12, 53.75, 29.72, 26.60, 26.54, 26.44, 16.24, 14.73.

**1-Benzyl-5-(phenylsulfonyl)-6-[hydroxypropyl]-2-[(ethoxycarbonyl)methylidene] piperidine (51).** TMS-I (0.464 g; 2.23 mmol) was added to slow vinylogous carbamate **11** (0.554; 1.10 mmol) in 3 mL of $CH_2Cl_2$ at 0 °C and the reaction was stirred for 6 h. The mixture was diluted with 15 mL of $CH_2Cl_2$ and 5 mL of sodium bisulfite was added to hydrolyze the excess TMS-I. The organic layer was washed with brine and dried over $MgSO_4$. Flash chromatography (9:1, diethyl ether/petroleum ether) gave 0.374 g (81%) of **51** as a yellow oil. Anal. Calcd for $C_{25}H_{31}NO_5S$: C, 65.62; H, 6.83; N, 3.06. Found: C, 65.39; H, 6.76; N, 2.98. $R_f$ = 0.17 (diethyl ether). IR 3485 $cm^{-1}$. $^1H$ NMR δ 7.76 (d, J = 6.2 Hz, 2H), 7.64 (t, J = 6.0 Hz, 1H), 7.51 (t, J = 5.5 Hz, 2H), 7.33 (m, 5H), 4.71 (s, 1H), 4.28 (m, 3H), 3.99 (m, 2H), 3.93 (m, 1H), 3.51 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.18 (m, 1H), 1.94 (m, 3H), 1.67 (m, 2H), 1.40 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). $^{13}C$ NMR δ 168.44, 160.93, 136.65, 135.72, 133.95, 129.21, 128.79, 128.53, 127.47, 127.33, 88.10, 63.78, 61.78, 58.58, 55.82, 55.04, 32.92, 27.97, 23.35, 20.39, 14.55.

**1-Benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methyl]-piperidine (52).** Vinylogous carbamate **11** (1.08 g; 1.97 mmol) was dissolved in 7 mL

of methanol and the pH was adjusted to 4 with acetic acid. $NaCNBH_3$ (0.124 g; 1.97 mmol) was added and the reaction bubbled and became warm. After 3 h the reaction mixture was diluted with ethyl acetate and washed with 20% NaOH, saturated $NaHCO_3$ and brine. The solvent was removed *in vacuo* to provide 1.05 g pure **52** in 97% yield. Anal. Calcd for $C_{32}H_{39}NO_5S$: C, 69.91; H, 7.15; N, 2.55. Found: C, 69.87; H, 7.11; N, 2.50.

**52** (fast band): $R_f$ = 0.60 (diethyl ether). IR 1730 $cm^{-1}$. $^1H$ NMR δ 7.88 (m, 2H), 7.53 (m, 5H), 7.29 (m, 8H), 4.55 (m, 3H), 4.10 (m, 2H), 3.80 (m, 1H), 3.63 (m, 1H), 3.50 (m, 4H), 3.29 (m, 1H), 2.77 (m, 1H), 2.46 (m, 1H), 1.96 (m, 4H), 1.65 (m, 2H), 1.34 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). $^{13}C$ NMR δ 169.96, 139.05, 133.28, 129.31, 129.02, 128.98, 128.73, 128.41, 128.35, 128.30, 128.24, 128.19, 128.16, 128.09, 128.05, 127.79, 127.63, 127.54, 127.51, 127.31, 127.26, 126.90, 72.79, 70.32, 61.32, 57.84, 56.78, 52.37, 42.46, 29.16, 27.24, 22.04, 20.77, 20.28, 18.51.

**52** (slow band): $R_f$ = 0.55 (diethyl ether). IR 1725 $cm^{-1}$. $^1H$ NMR δ 7.80 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.30 (m, 10H), 4.42 (s, 2H), 4.08 (m, 2H), 3.77 (q, J = 14.1 Hz, 2H), 3.42 (m, 2H), 3.31 (m, 3H), 3.01 (m, 1H), 2.57 (m, 1H), 2.34 (m, 1H), 2.03 (m, 1H), 1.84 (m, 2H), 1.70 (m, 2H), 1.59 (m, 1H), 1.45 (m, 1H), 1.23 (t, J = 7.5 Hz, 3H). $^{13}C$ NMR δ 171.67, 139.46, 138.52, 138.49, 133.31, 129.00, 128.60, 128.52, 128.21, 128.13, 127.51, 127.34, 126.83, 72.78, 69.81, 61.53, 60.45, 54.38, 51.48, 50.67, 38.49, 27.11, 26.37, 23.16, 21.09, 14.23.

**1-Benzyl-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methyl]-piperidine (52H).** Vinylogous carbamate **11H** (1.32 g; 3.24 mmol) was dissolved in 7 mL of methanol and the pH was adjusted to 4 with acetic acid. $NaCNBH_3$ (0.204 g; 3.24 mmol) was added and the reaction bubbled and became warm. After 3 h, the reaction mixture was diluted with ethyl acetate and washed with 20% NaOH, saturated $NaHCO_3$ and brine. The solvent was removed *in vacuo* to provide 1.29 g pure **52H** in 97% yield. Anal. Calcd for $C_{26}H_{35}NO_3$: C, 70.71; H, 7.99; N, 3.17. Found: C, 70.32; H, 8.00; N, 3.57. $R_f$ = 0.74 (diethyl ether) $^1$H NMR δ 7.27 (m, 10H), 4.44 (s, 2H), 4.09 (m, 2H), 3.70 (m, 4H), 3.32 (m, 3H), 2.77 (m, 1H), 2.62 (m, 1H), 2.36 (m, 1H), 1.64 (m, 5H), 1.38 (m, 3H), 1.22 (m, 3H). $^{13}$C NMR δ 168.83, 141.51, 138.21, 128.67, 128.31, 127.59, 126.98, 126.43, 73.12, 71.02, 60.84, 54.87, 52.91, 50.99, 38.01, 29.17, 27.55, 25.89, 25.78, 22.08, 14.67.

**5-(Phenylsulfonyl)-6-[hydroxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine (53).** Piperidine **52** (1.18 g; 2.14 mmol) was dissolved in 4 mL of ethanol and excess Raney-Nickel W-2 was added. The reaction was stirred for 6 h and an additional portion of Raney-Nickel was added followed by stirring for 18 h. The reaction was filtered through Celite and the solvent removed *in vacuo*. The organic residue was dissolved in 40 mL of ethyl acetate and washed with $H_2O$, saturated $Na_2CO_3$, and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 0.657 g (83%) of **53** as a colorless oil. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 59.51; H, 7.37; N, 3.79. Found: C, 59.19; H, 7.65; N, 3.54.

**53** (fast band): $R_f$ = 0.15 (diethyl ether). $^1$H NMR δ 7.88 (d, J = 5.2 Hz, 2H), 7.68 (t, J = 5.1 Hz, 1H), 7.59 (t, J = 5.9 Hz, 2H), 4.12 (m, 1H), 3.68 (m, 1H), 3.53 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 2.73 (m, 2H), 2.61 (m, 2H), 2.32 (m, 1H), 1.94 (m, 4H), 1.18 (m, 1H), 1.61 (m, 2H), 1.52 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H). $^{13}$C NMR δ 133.58, 129.16, 128.98, 128.28, 63.01, 60.29, 57.76, 46.73, 41.99, 31.84, 25.16, 20.36, 19.80, 13.18.

**53** (slow band): $R_f$ = 0.12 (diethyl ether). IR 3505 cm$^{-1}$. $^1$H NMR δ 7.88 (d, J = 4.9 Hz, 2H), 7.66 (t, J = 4.1 Hz, 1H), 7.58 (t, J = 4.9 Hz, 2H), 4.14 (m, 3H), 3.55 (m 4H), 3.27 (m, 2H), 2.84 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 2.01 (m, 2H), 1.70 (m 3H), 1.43 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). $^{13}$C NMR δ 171.43, 137.67, 133.73, 129.26, 128.33, 62.40, 61.10, 60.67, 50.64, 45.89, 41.01, 30.84, 30.76, 26.77, 19.77, 14.26.

**6-[Hydroxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine (53H).** Piperidine **52H** (1.01 g; 2.48 mmol) was dissolved in 4 mL of ethanol and excess Raney-Nickel W-2 was added. The reaction was stirred for 6 h and an additional portion of Raney-Nickel was added followed by stirring for 18 h. The reaction was filtered through Celite and the solvent removed *in vacuo*. The organic residue was dissolved in 40 mL of ethyl acetate and washed with $H_2O$, saturated $Na_2CO_3$, and brine, then dried over $MgSO_4$ and solvent removed *in vacuo* to yield 0.232 g (41%) of **53H** as a colorless oil. HRMS m/z Calcd for $C_{12}H_{23}NO_3$: 228.1600, found: 228.1599. $R_f$ = 0.15 (diethyl ether). IR 3495 cm$^{-1}$. $^1$H NMR 4.14 (m, 2H), 3.58 (m, 3H), 2.96 (m, 1H), 2.62 (m, 1H), 2.41 (m, 2H), 1.84 (m,

2H), 1.73 (m, 1H), 1.61 (m, 4H), 1.45 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.16 (m, 2H). $^{13}$C NMR δ 172.19, 62.85, 60.48, 56.44, 53.33, 41.09, 35.73, 31.74, 31.52, 29.70, 24.46, 14.18.

**8-(Phenylsulfonyl)-5-[(ethoxycarbonyl)methyl]indolizidine (54).** Piperidine **53** (0.025 g; 0.07 mmol) was dissolved in 7 mL of THF and cooled to -78° C. Trifluoromethane sulfonic anhydride (0.022 g; 0.08 mmol) was added and stirred for 10 minutes. The -78 °C bath was removed and triethylamine (0.018 g; 0.18 mmol) added and the reaction allowed to equilibrate to room temperature. The mixture was diluted with 10 mL of ethyl acetate and washed with saturated $NaHCO_3$, and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate) yielded 0.023 g (96%) of **54** as a colorless oil. Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.29; H, 7.27; N, 3.81.

**54** (fast band): $R_f$ = 0.46 (diethyl ether). IR 2800 cm$^{-1}$. $^1$H NMR δ 7.89 (d, J = 5.3 Hz, 2H), 7.65 (t, J = 5.0 Hz, 1H), 7.56 (t, J = 5.9 Hz, 2H), 3.28 (m, 2H), 2.57 (m, 4H), 1.82 (m, 4H), 1.48 (m, 2H), 1.02 (m, 3H). $^{13}$C NMR δ 133.28, 129.04, 128.98, 128.30, 62.11, 57.88, 47.58, 43.61, 21.77, 20.63, 17.82, 13.96, 12.43.

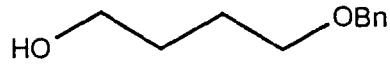
**54** (slow band): $R_f$ = 0.36 (diethyl ether). IR 2795 cm$^{-1}$. $^1$H NMR δ 7.89 (d, J = 4.0 Hz, 2H), 7.66 (t, J = 4.1 Hz, 1H), 7.57 (t, J = 4.3 Hz, 2H), 4.10 (m 2H), 3.56 (m, 1H), 3.45 (m, 1H), 2.85 (m, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 2.28 (m, 1H), 2.16 (m, 1H),

1.70 (m, 6H), 1.25 (m, 3H). $^{13}$C NMR δ 172.54, 138.04, 133.60, 129.02, 128.59, 66.84, 60.54, 53.50, 51.35, 48.59, 30.44, 28.75, 27.92, 21.04, 20.70, 14.25.

**5-[(Methoxycarbonyl)methyl]indolizidine (55).** Indolizidine **54** (0.358 g; 1.02 mmol) was dissolved in 5 mL of methanol and excess 6% Na/Hg added. The reaction was monitored by TLC for consumption of starting material. After 5 h, the mixture was filtered into 3 mL of methanolic HCl to capture the volatile indolizidine as the hydrochloride salt. The solvent was removed *in vacuo* followed by partitioning between diethyl ether and 20% KOH to liberate the free base. Removal of solvent yielded 0.080 g of indolizidine **55** (38%). HRMS m/z Calcd for $C_{11}H_{19}NO_2$: 197.1416, found: 197.1416. $R_f$ = 0.38 (diethyl ether). IR 2765 cm$^{-1}$. $^1$H NMR δ 3.68 (s, 3H), 3.61 (m, 1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.42 (m, 4H), 1.88-1.12 (m, 7H). $^{13}$C NMR δ 173.81, 54.99, 52.53, 51.54, 49.03, 31.33, 30.60, 29.15, 28.81, 20.72, 19.29.

# APPENDIX

# SPECTRAL DATA

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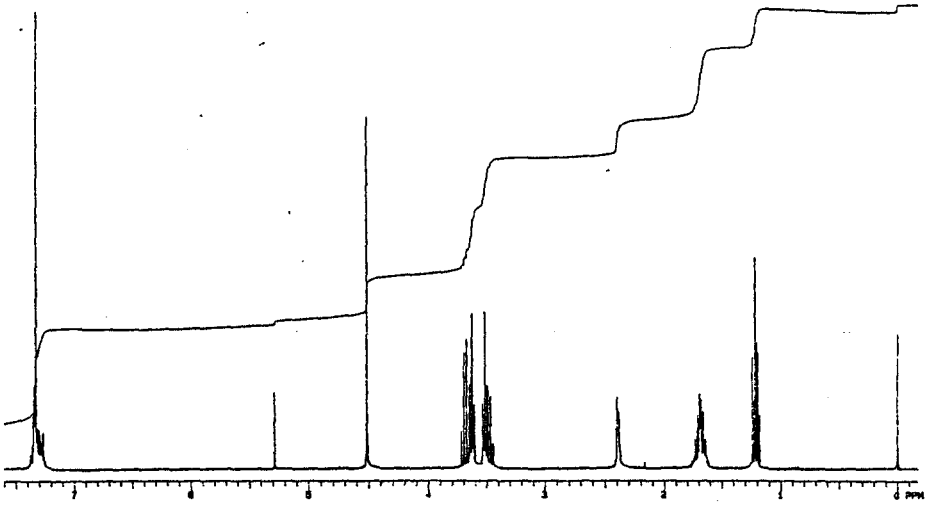
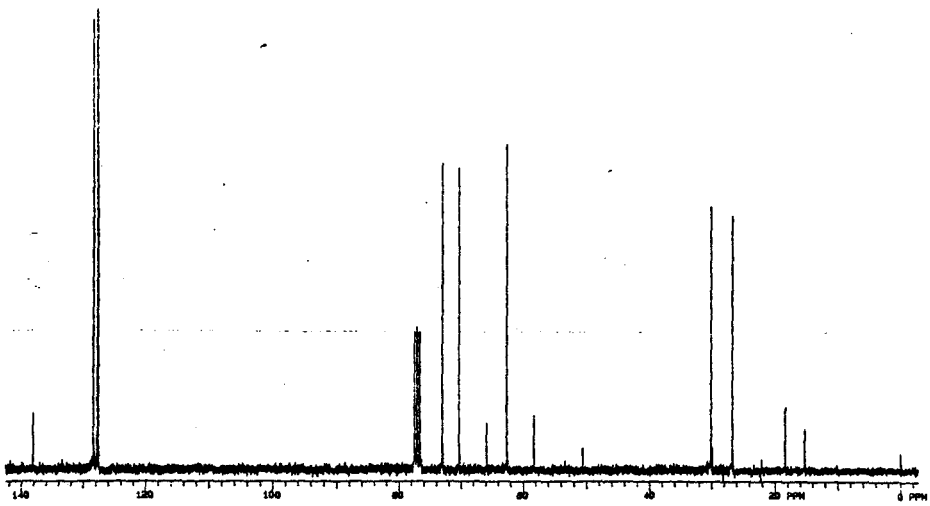
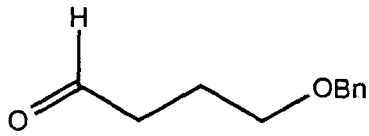




$^{1}H$ NMR and $^{13}C$ NMR O-benzyl 1,4-butanediol

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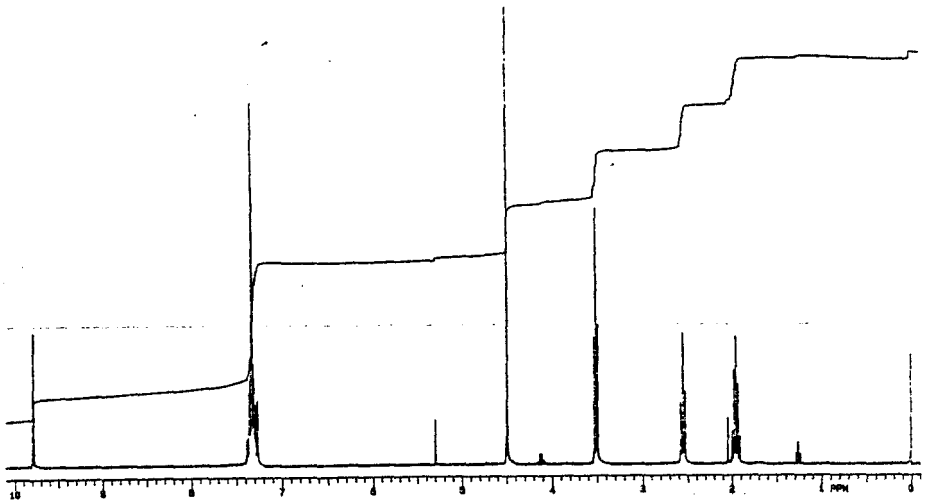
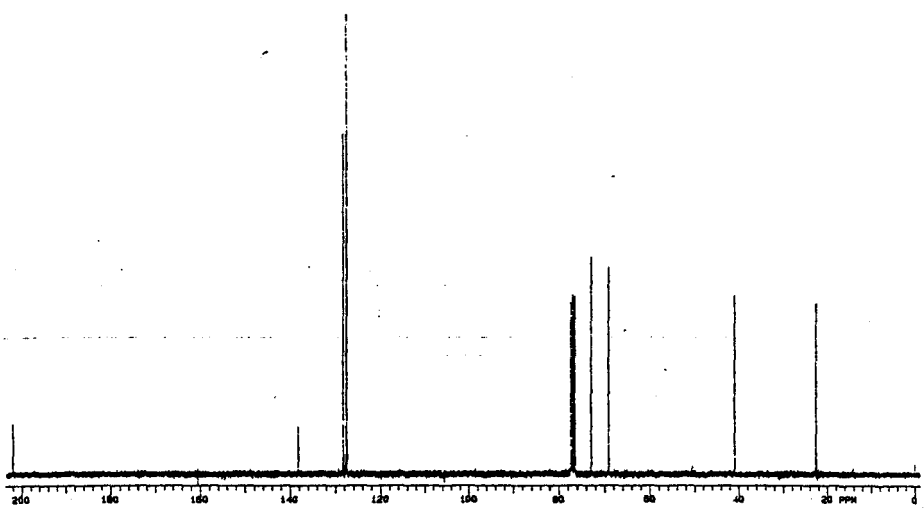
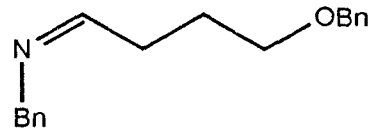




$^{1}H$ NMR and $^{13}C$ NMR 4-(benzyloxy)-butan-1-al

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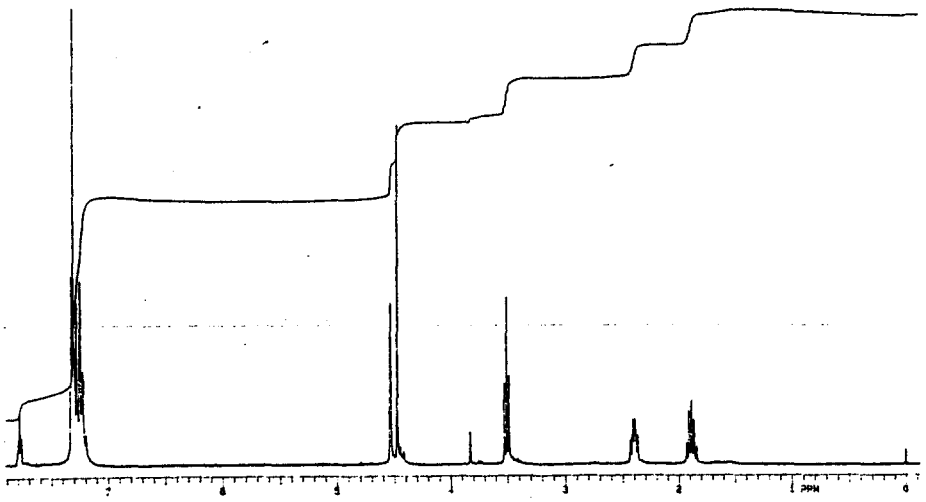
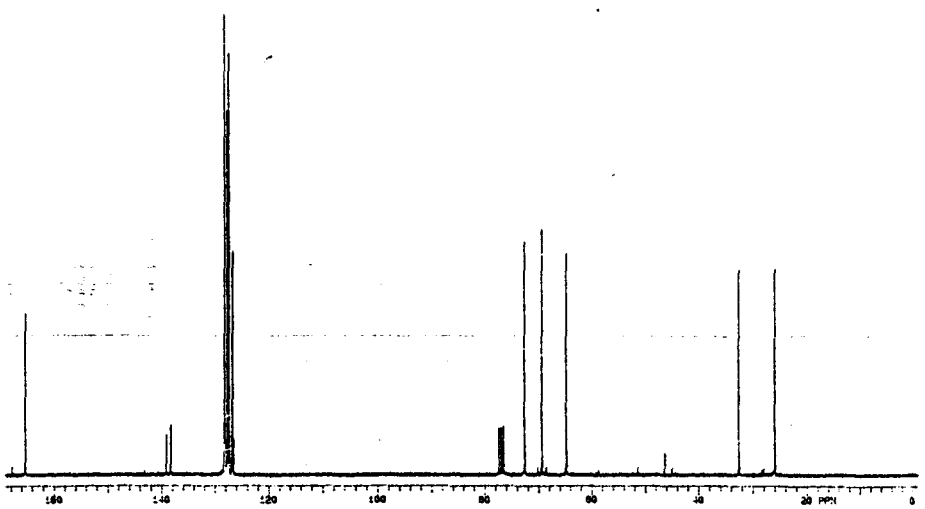
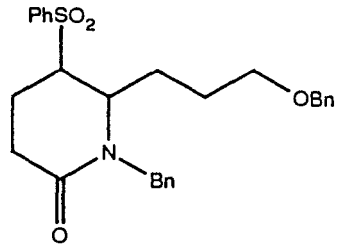
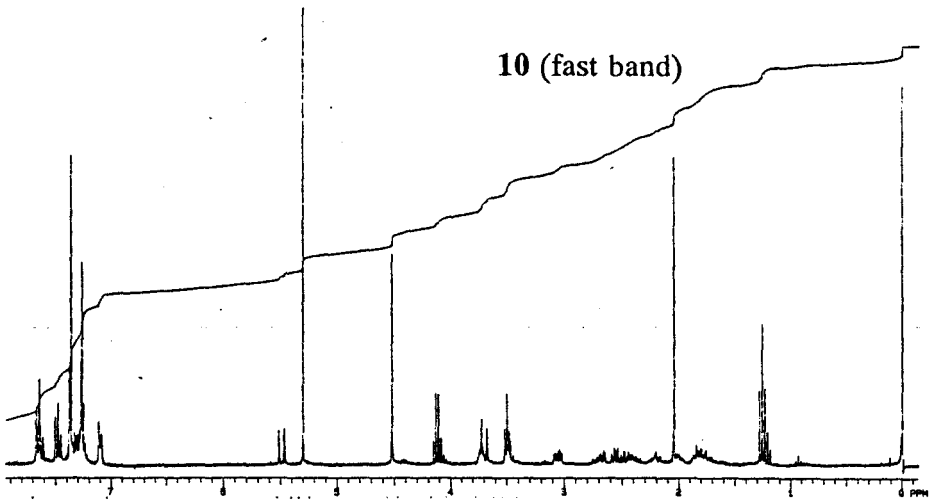
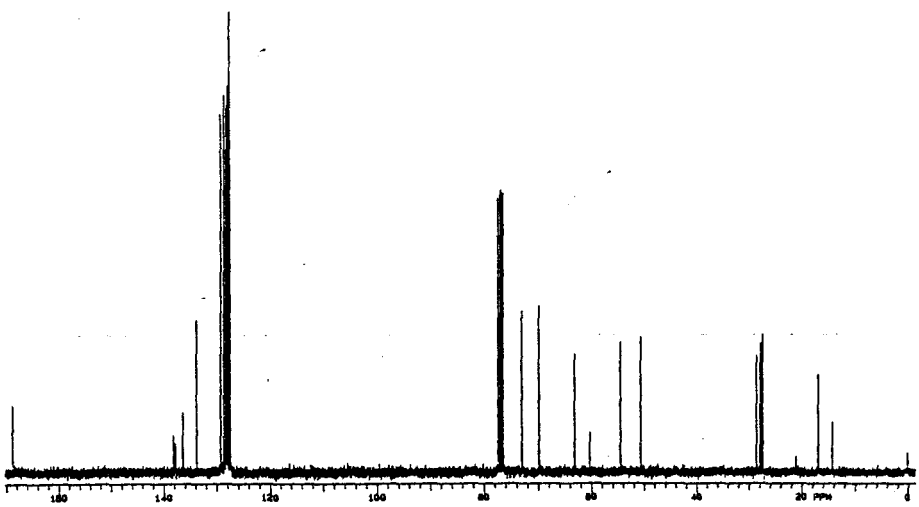




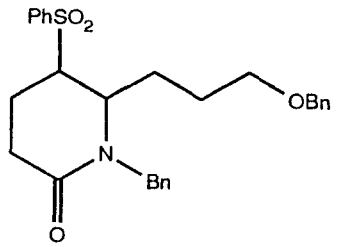
$^{1}H$ NMR and $^{13}C$ NMR N-benzylidene-4-(O-benzyl)-butanal

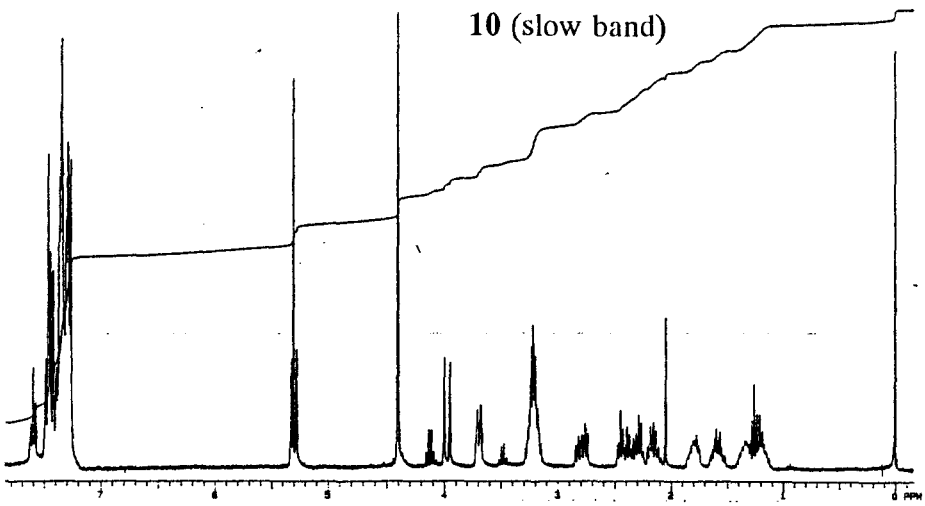


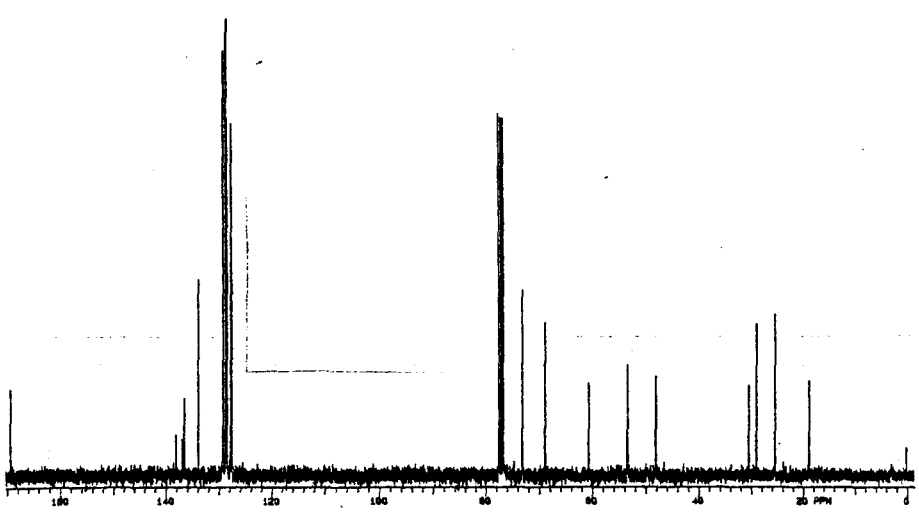



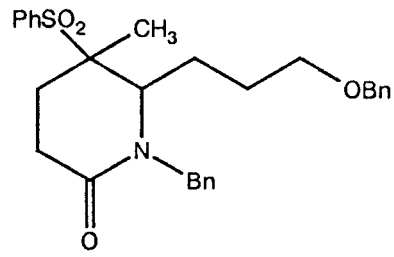
$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl]-2-piperidinone (fast band)



$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl] 2-piperidinone (slow band)

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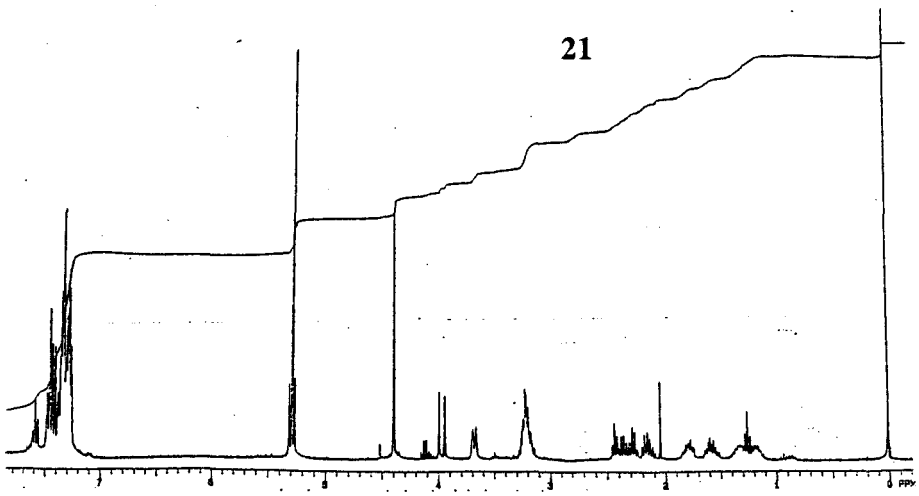
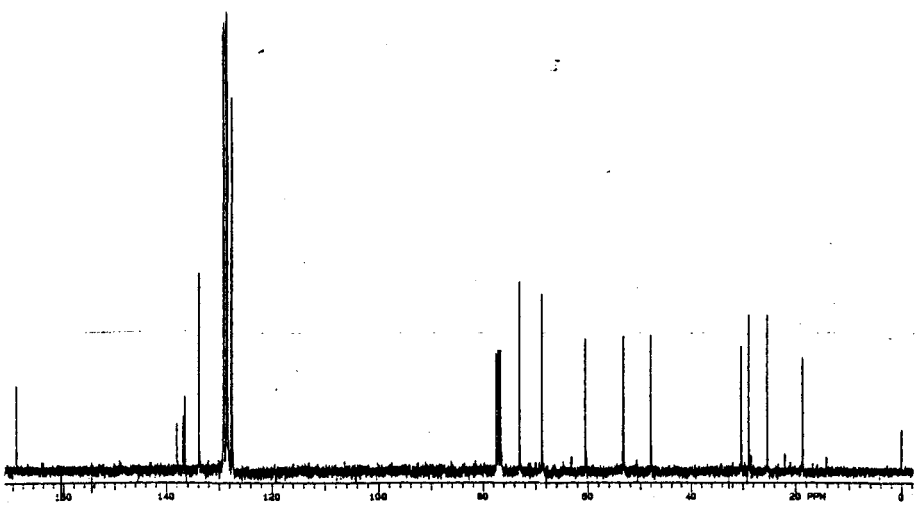
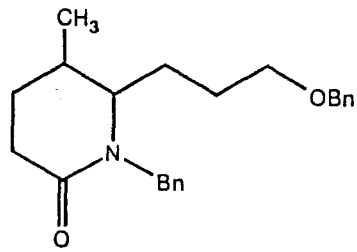




$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-5′-methyl-6-[3-benzyloxypropyl] 2-piperidinone

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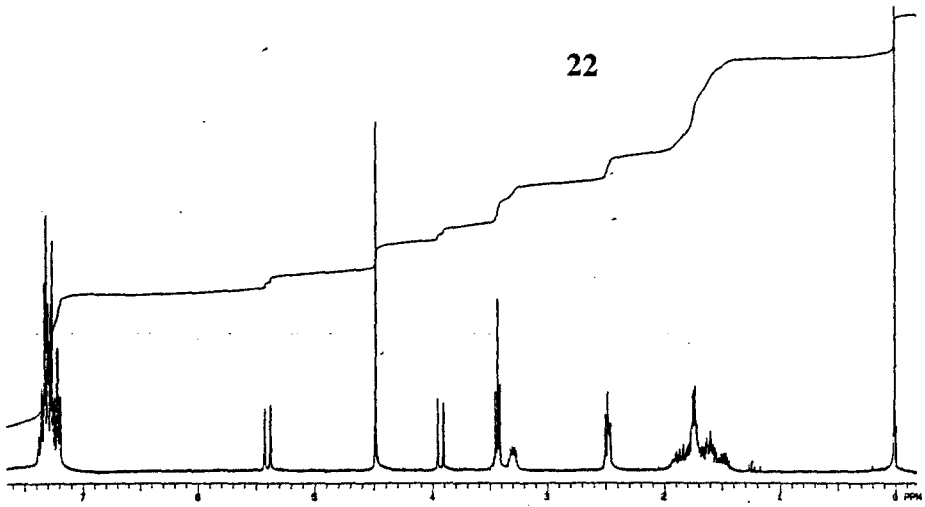
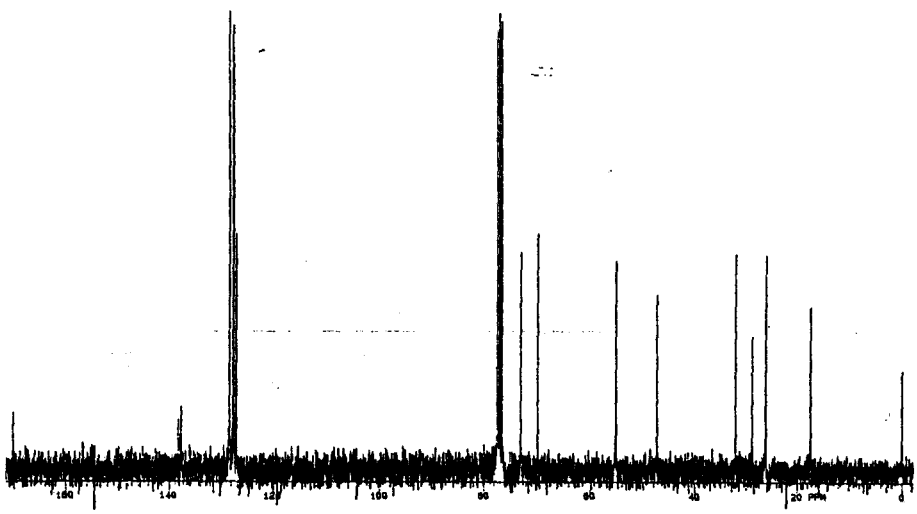
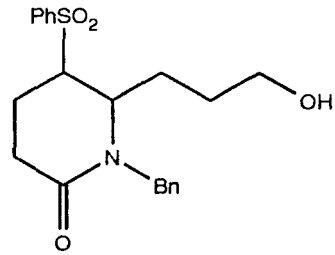
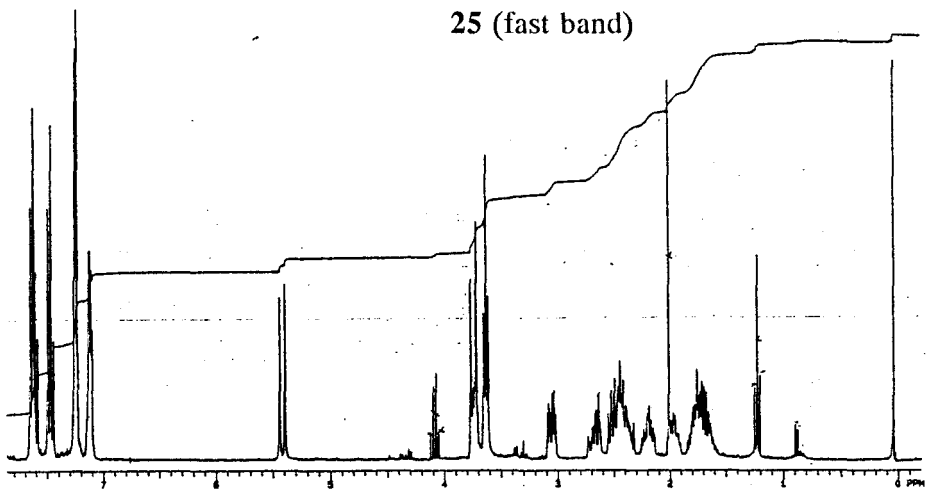


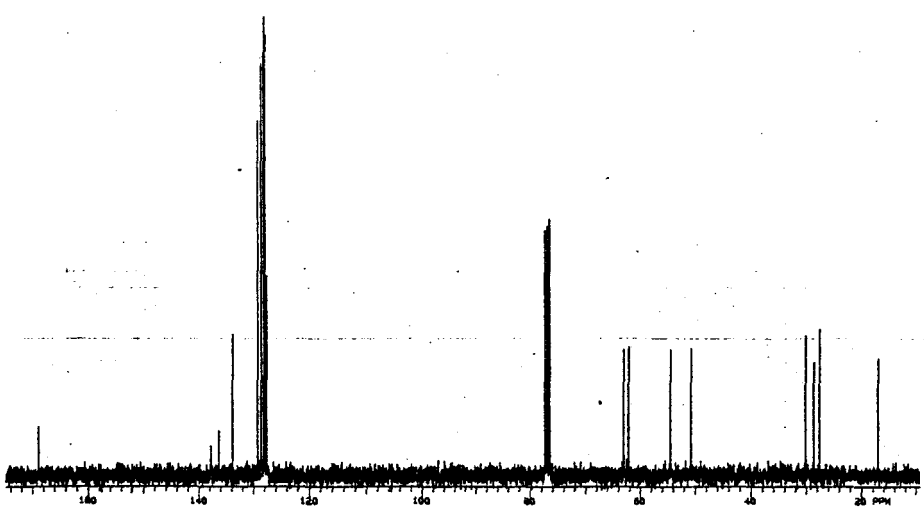


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-methyl-6-[3-benzyloxypropyl]-2-piperidinone

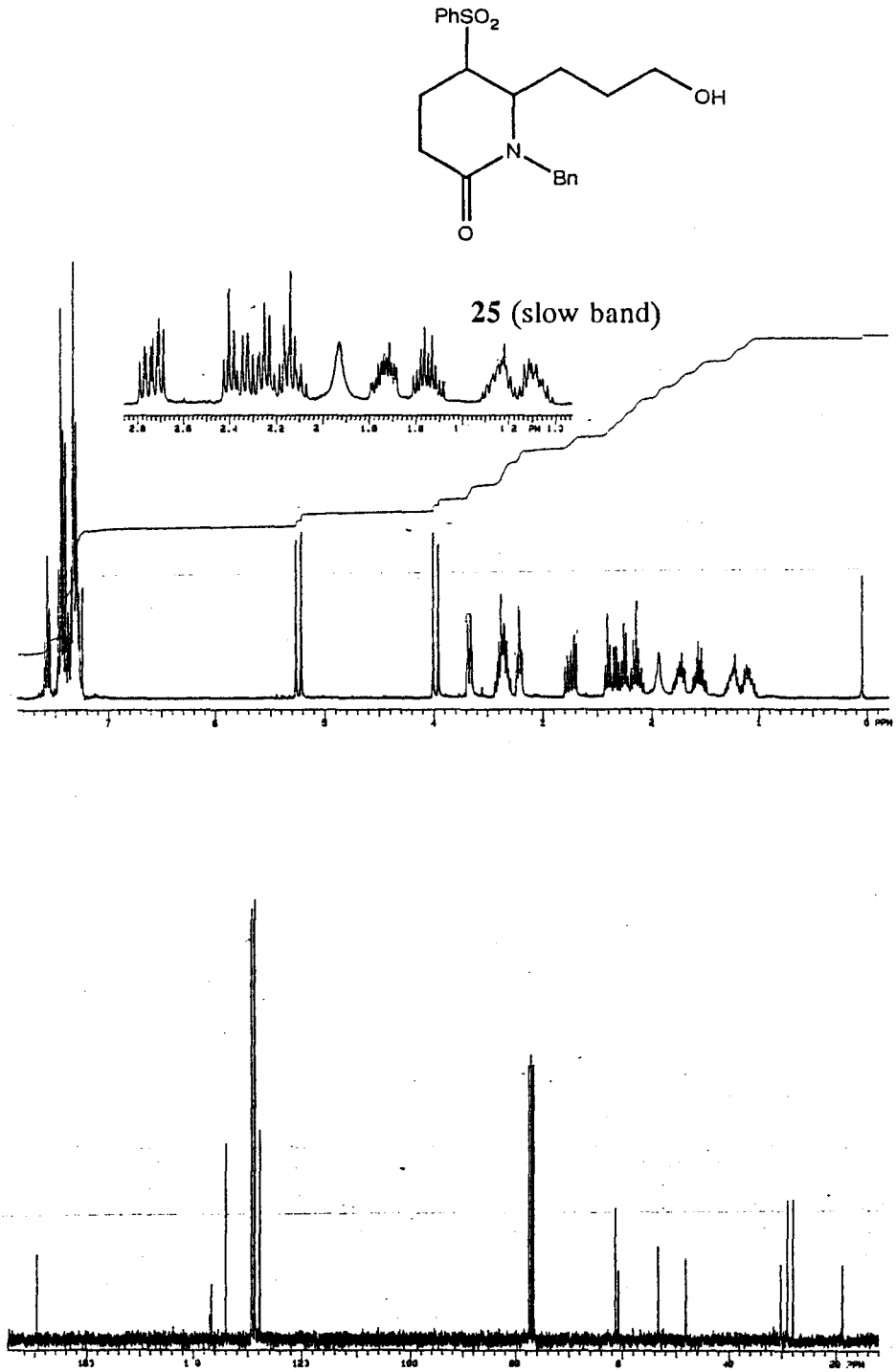



**25** (fast band)





$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-hydroxypropyl] 2-piperidinone(fast band)

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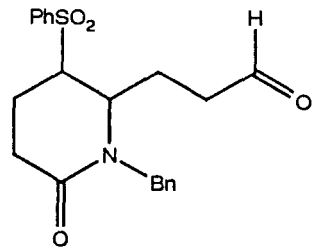


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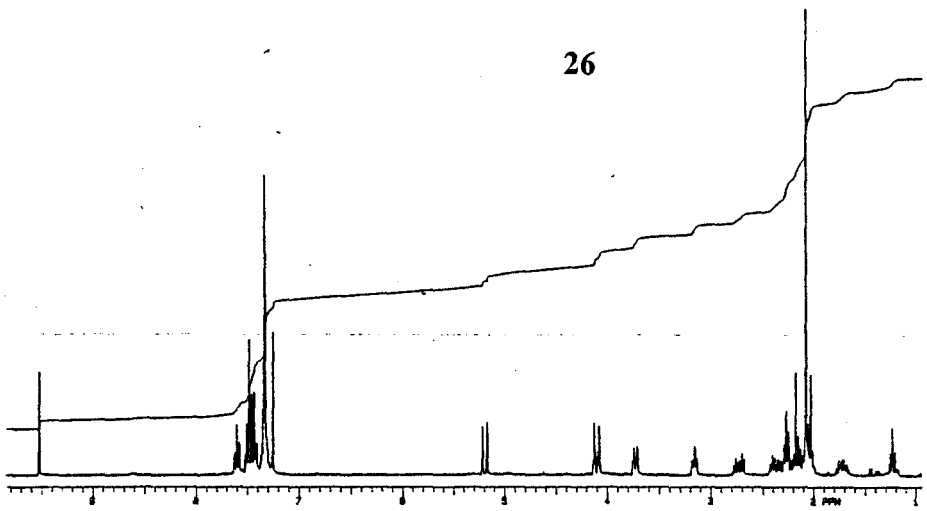
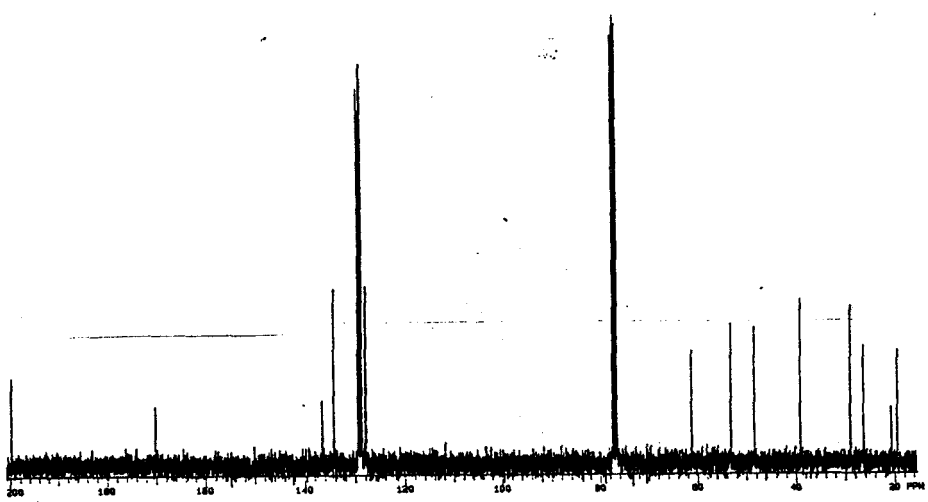
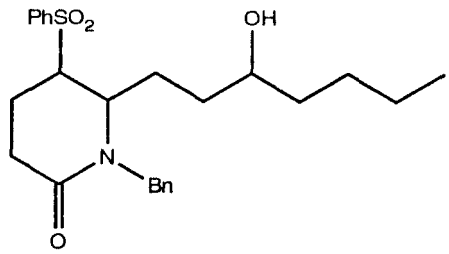




$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[propa-3-al]-2-piperidinone

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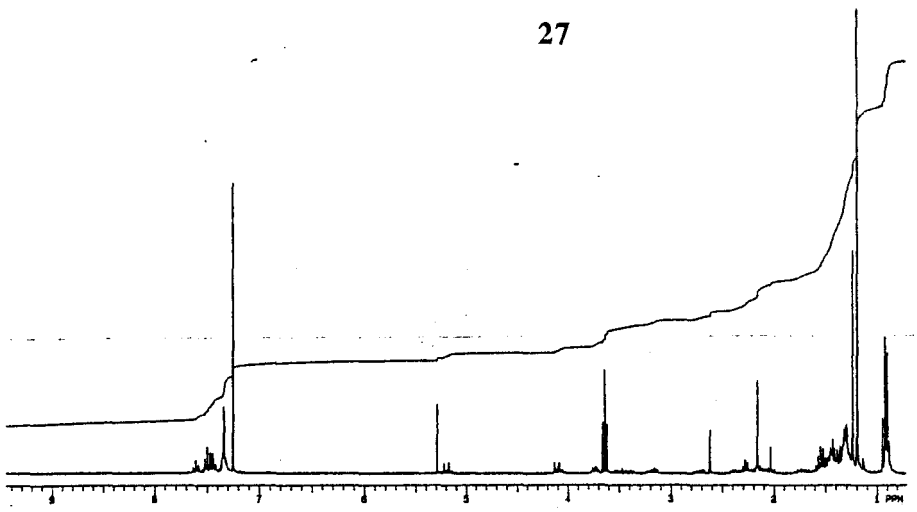
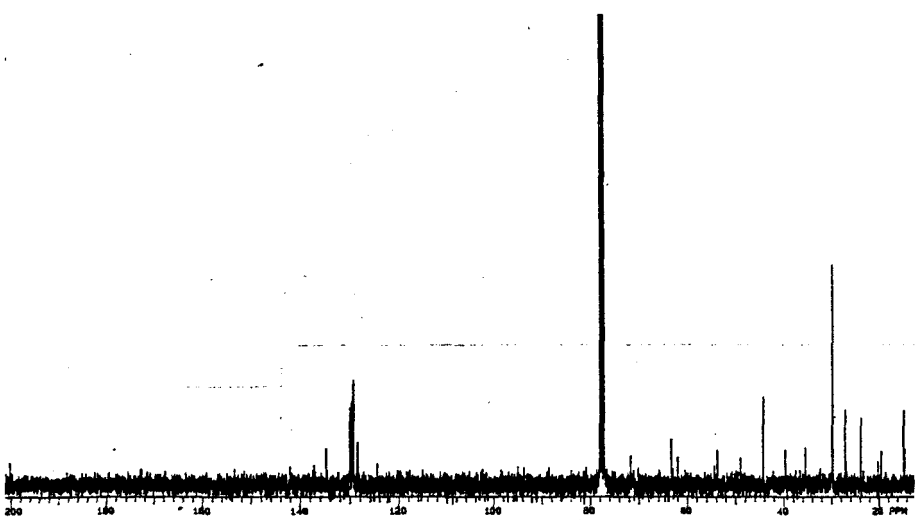
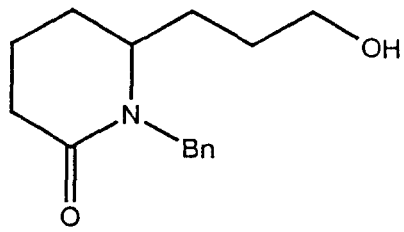




$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-hydroxyheptane] 2-piperidinone

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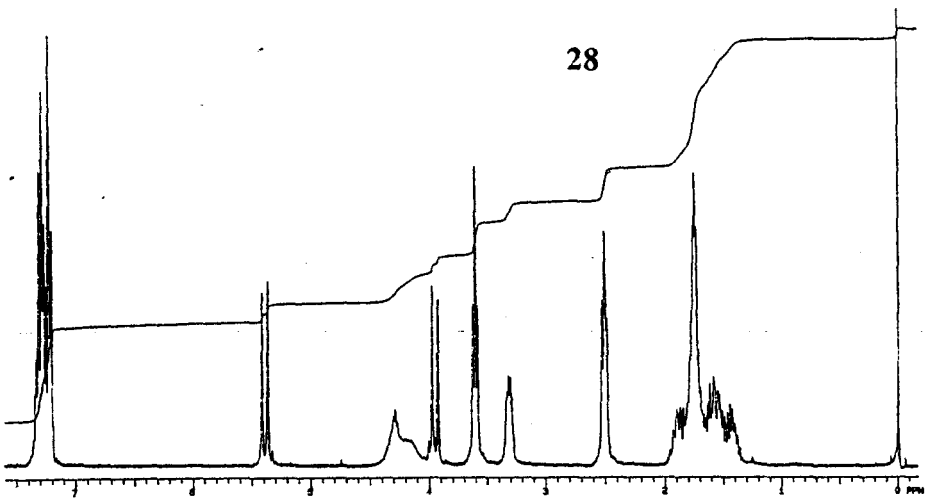
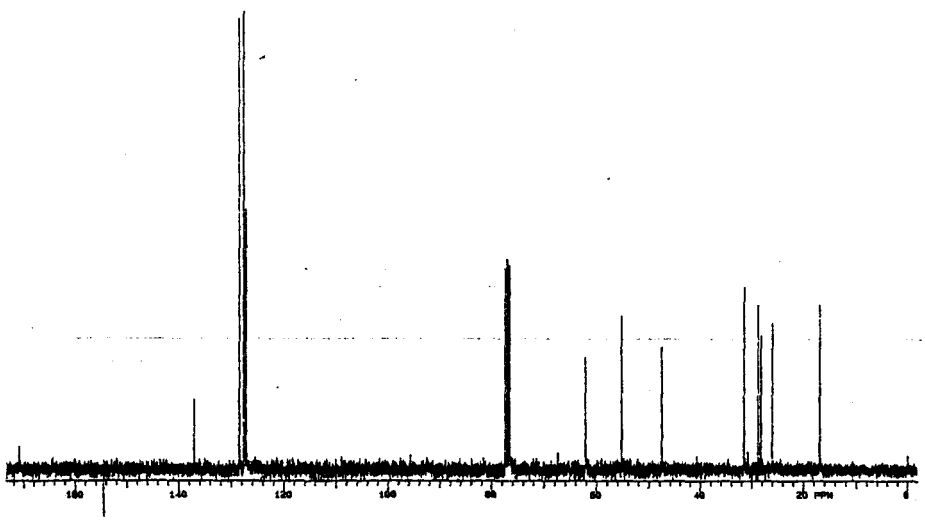
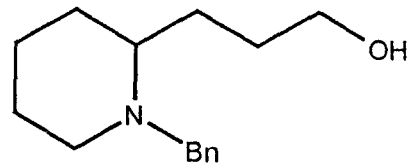




$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-hydroxypropyl]-2-piperidinone

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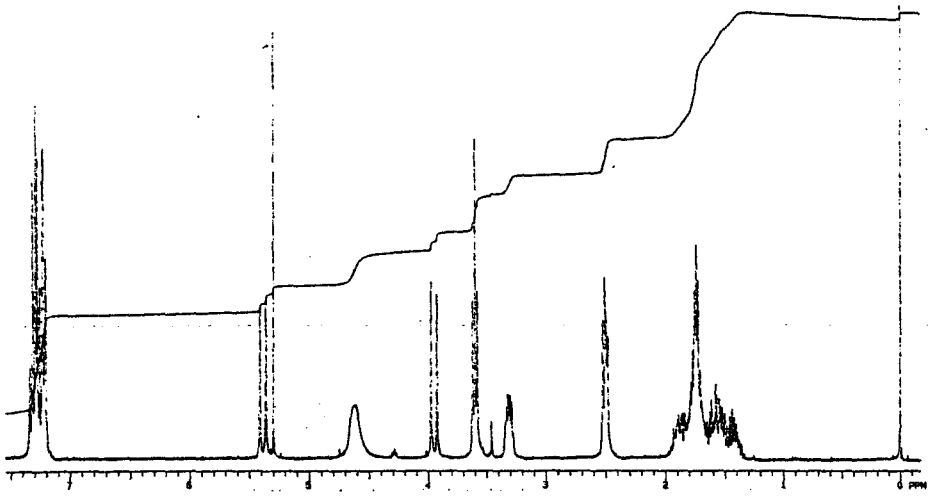
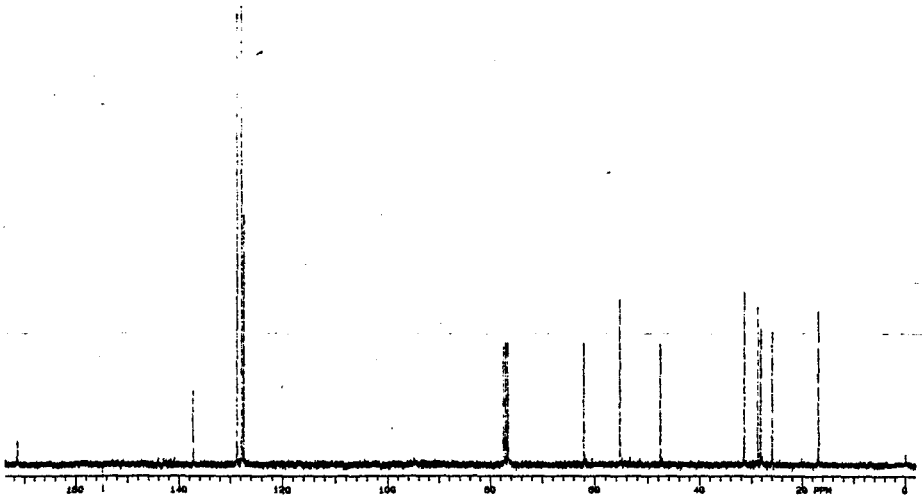
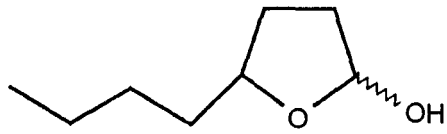




$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-hydroxypropyl]piperidine

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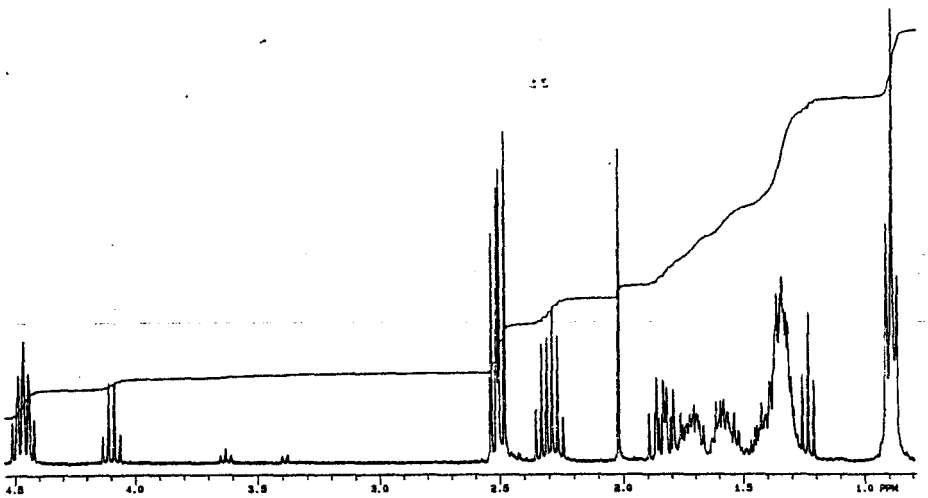
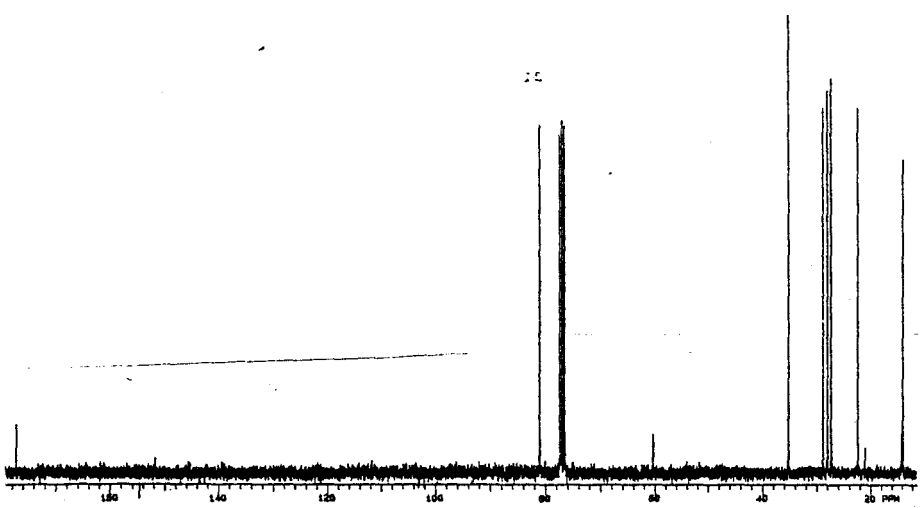
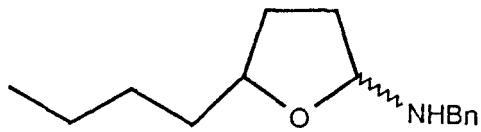




$^{1}H$ NMR and $^{13}C$ NMR γ-octanoic lactol

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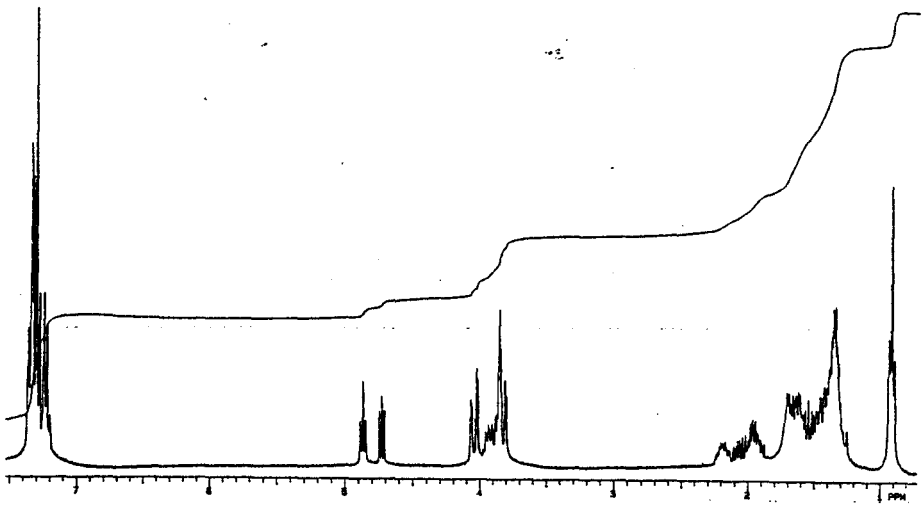
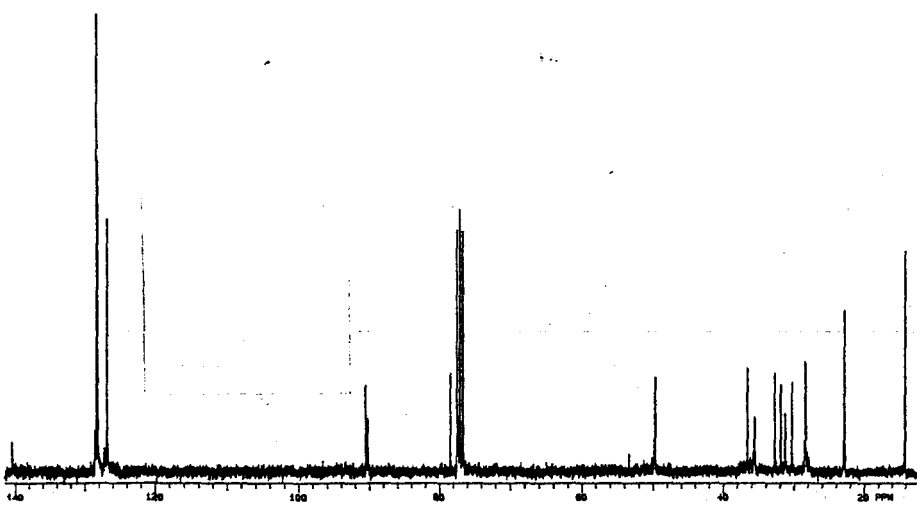
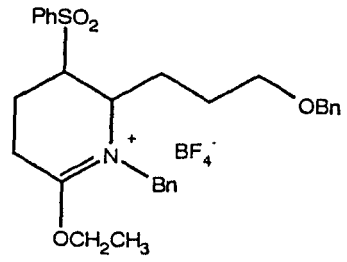
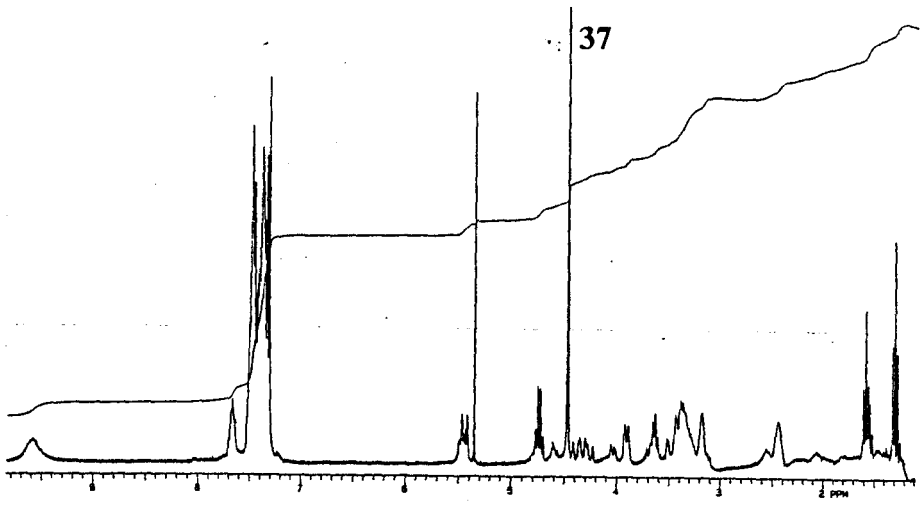
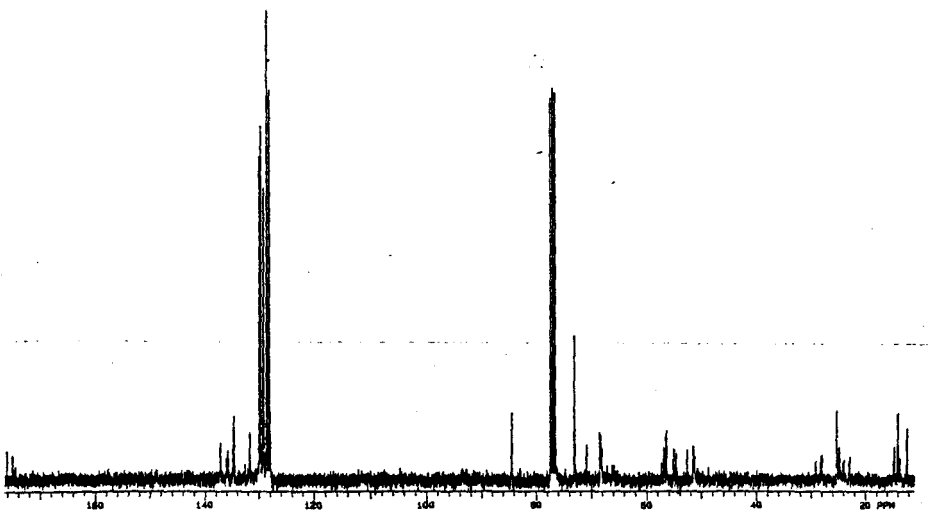




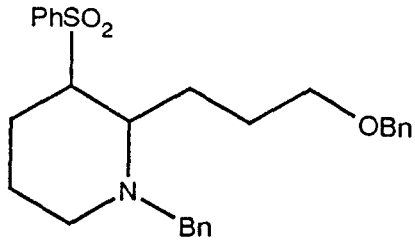
$^{1}H$ NMR and $^{13}C$ NMR N-benzyl-2-amino-5-butyl-terahydrofuran



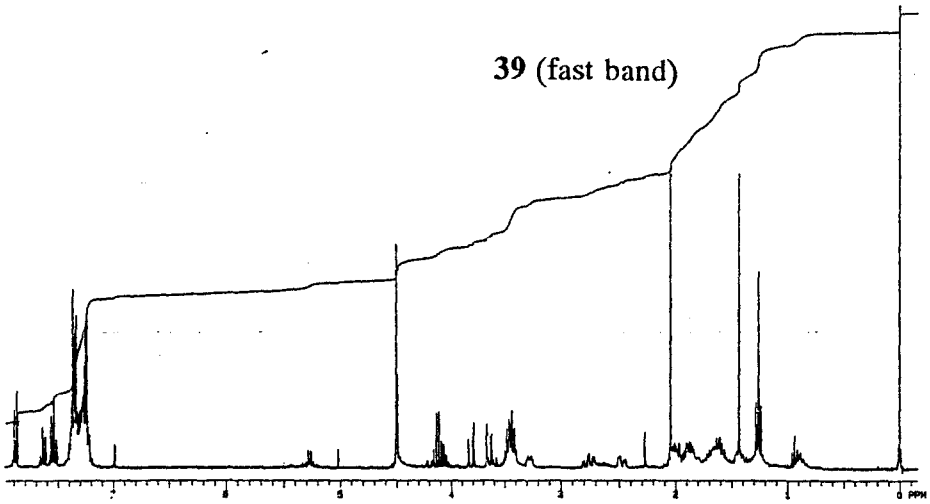



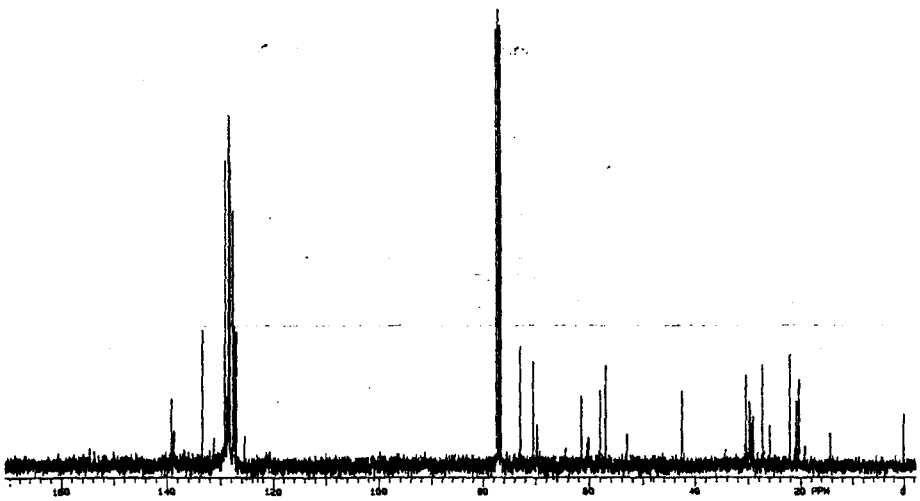



$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-benzyloxypropyl]-2-ethoxy-5-(phenylsulfonyl) piperidinium tetrafluoroborate

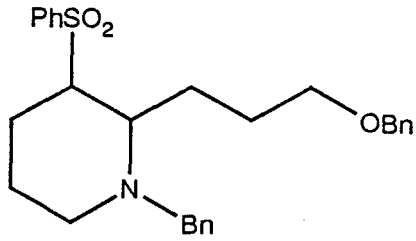


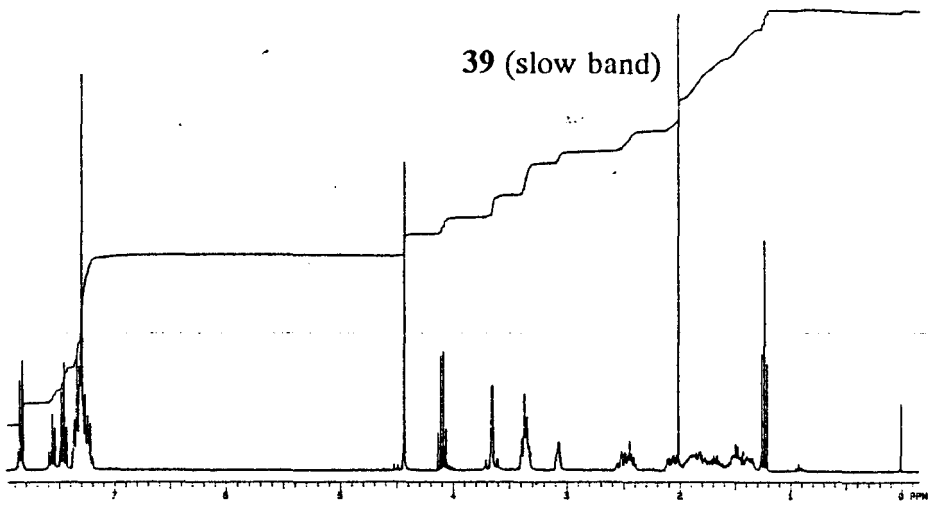

**39** (fast band)

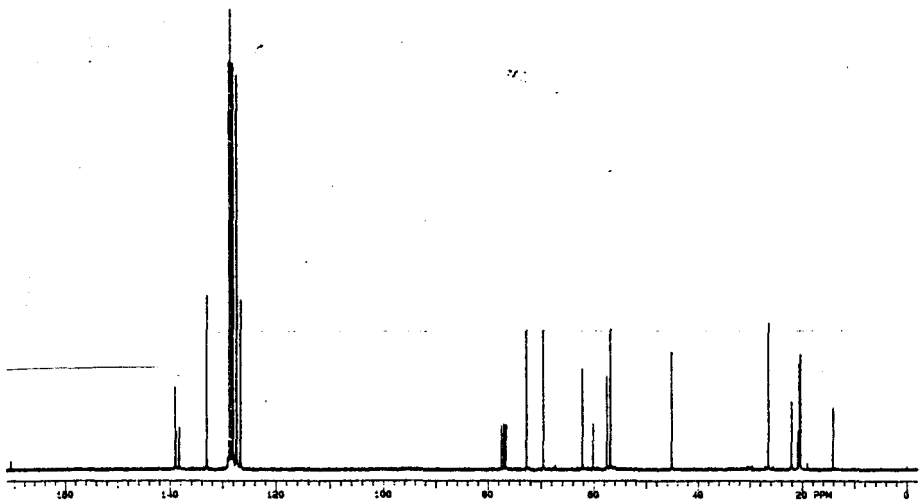




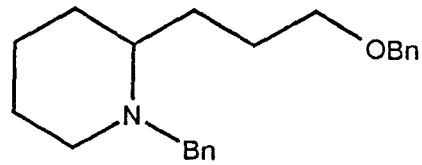
$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-2-[3-benzyloxypropyl]-3-(phenylsulfonyl)piperidine (fast band)



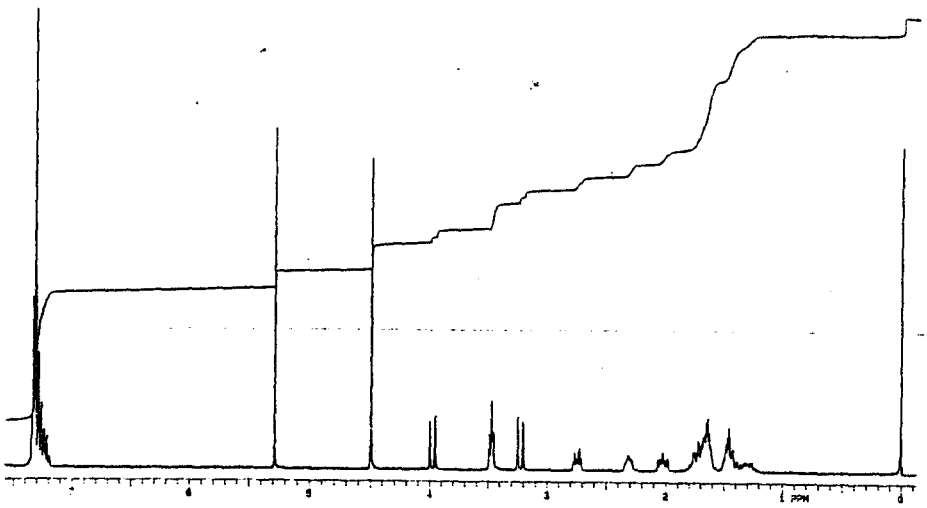



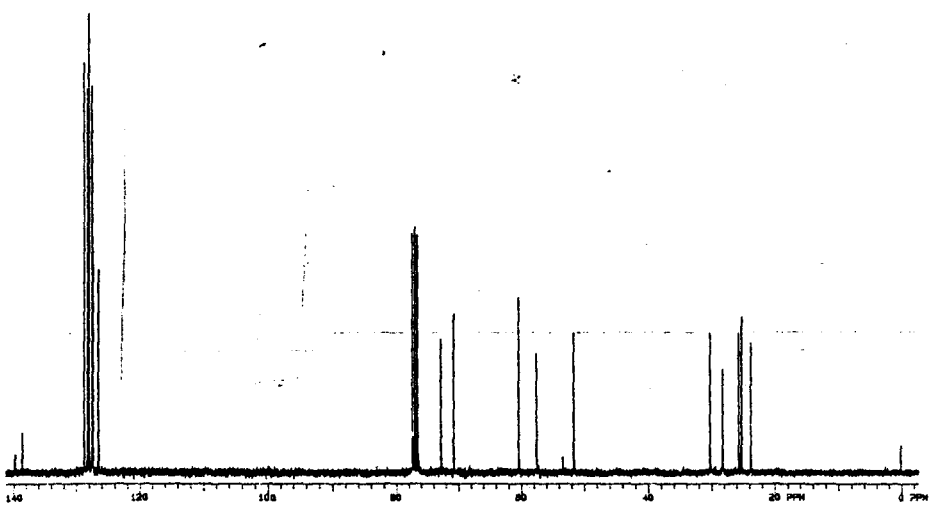



$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-2-[3-benzyloxypropyl]-3-(phenylsulfonyl)piperidine (slow band)

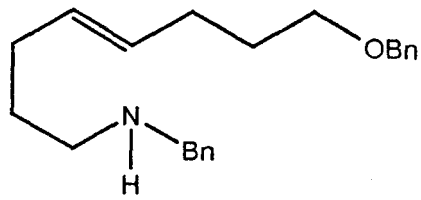



**41**

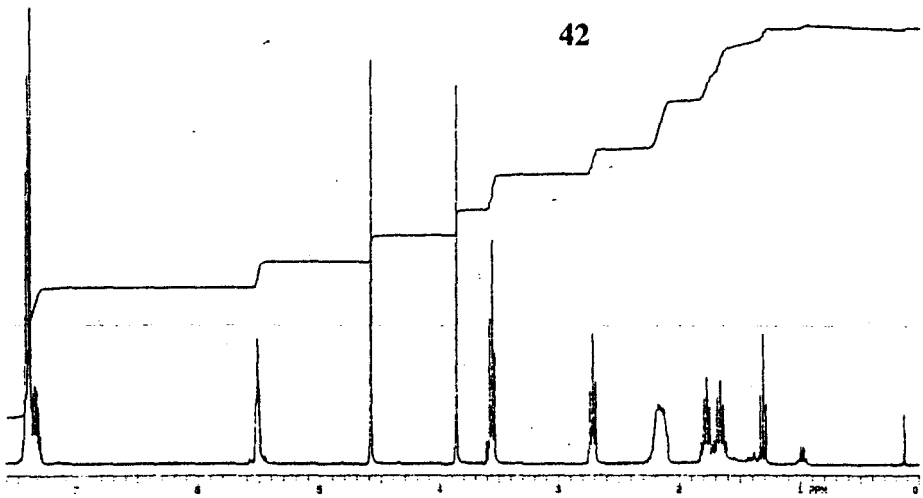


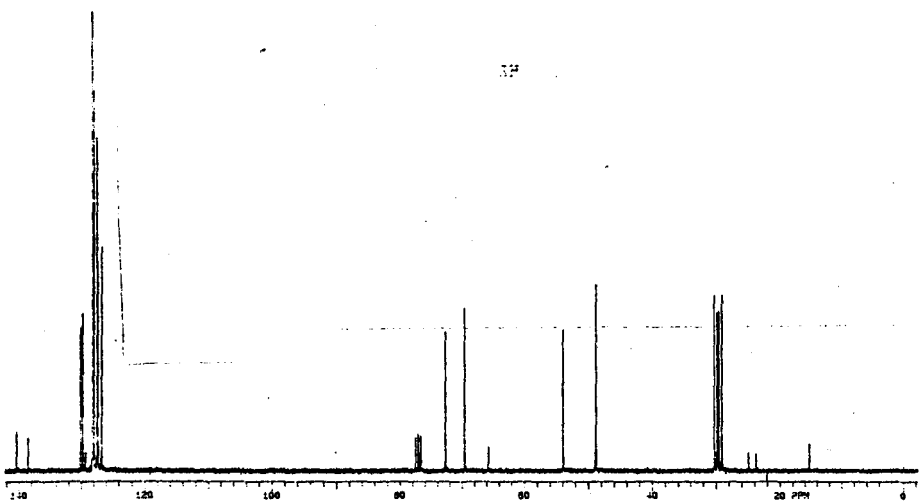


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-benzyloxypropyl]piperidine

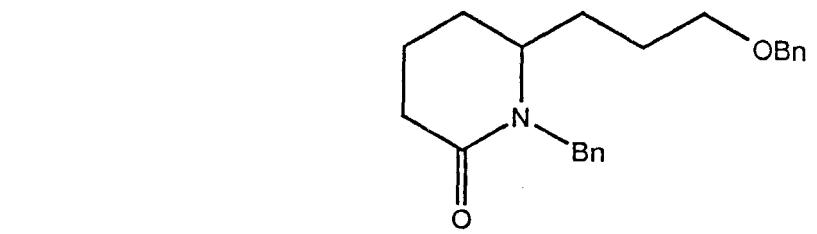



**42**

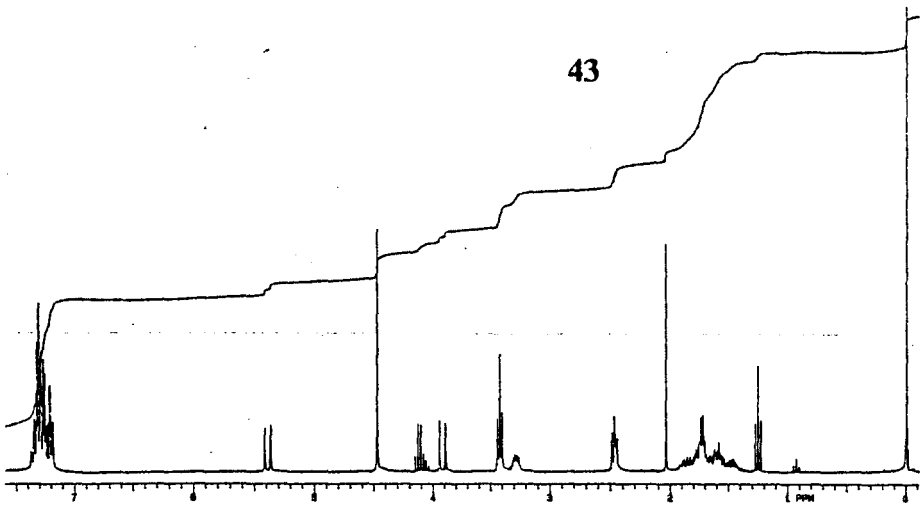


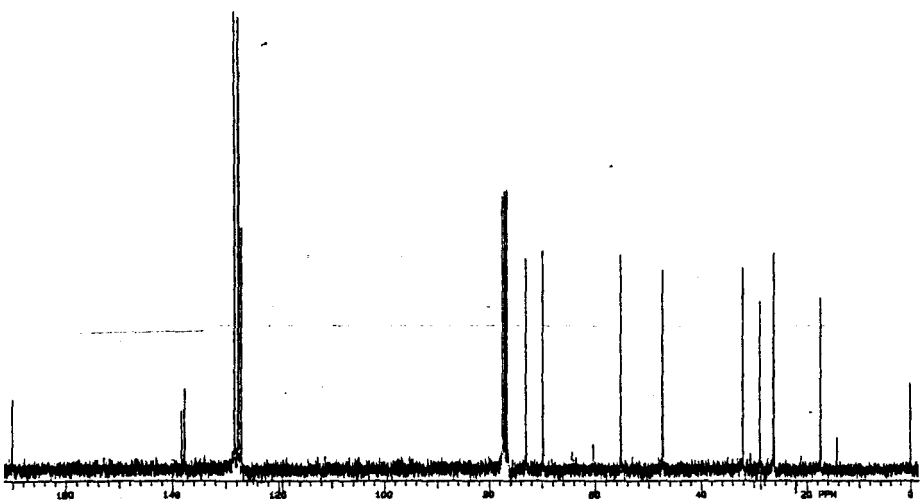


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-8-benzyloxy-oct-4-ene

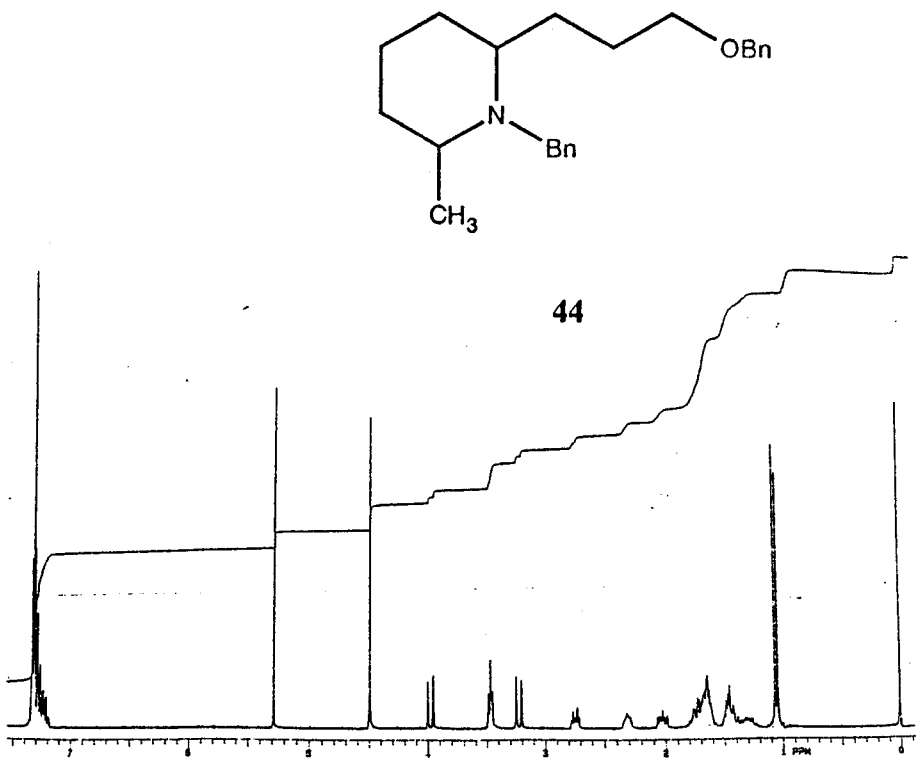



**43**

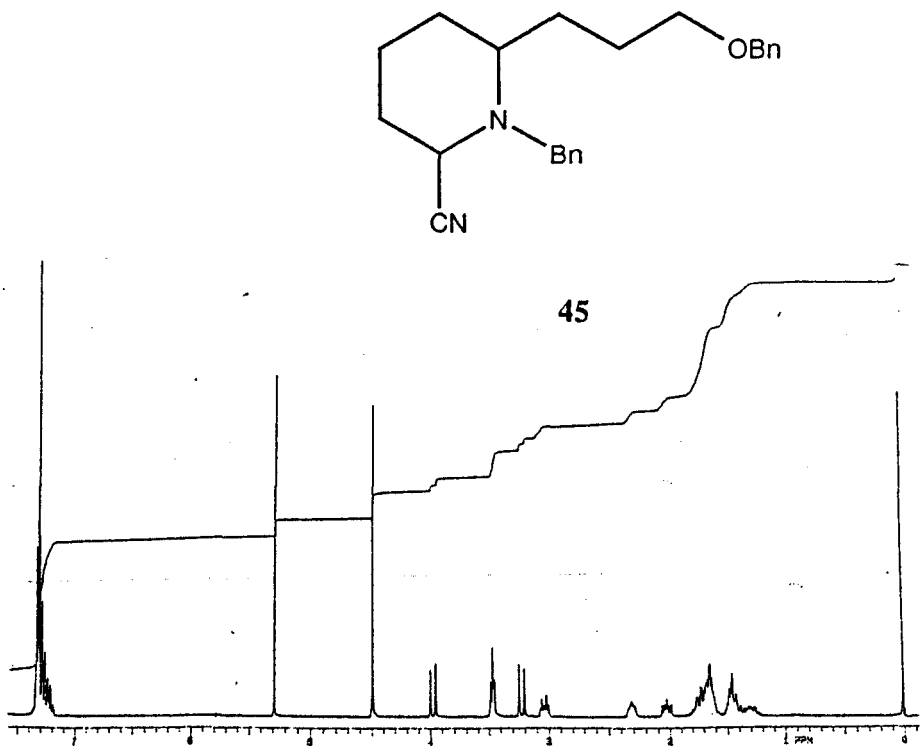




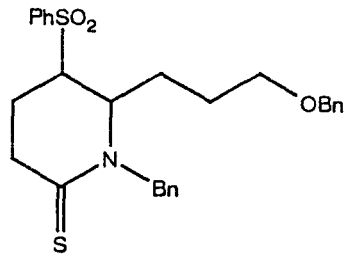
$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-benzyloxypropyl]-2-piperidinone

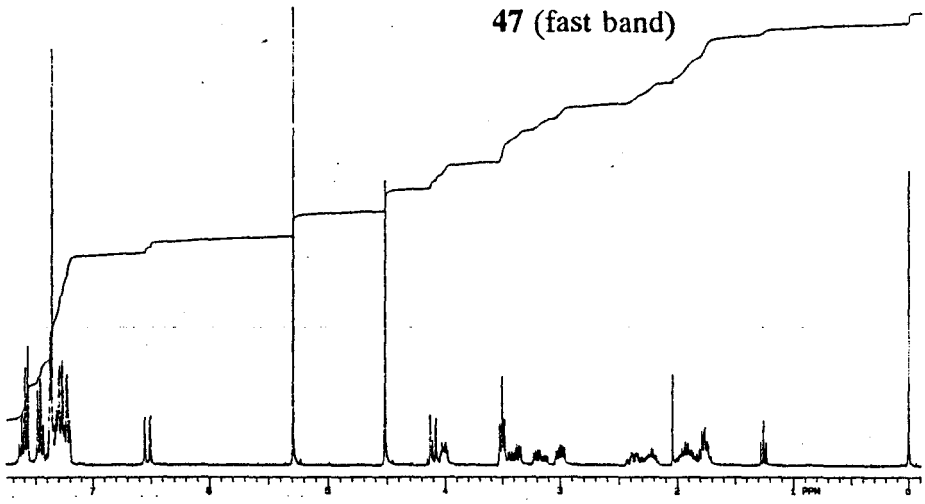


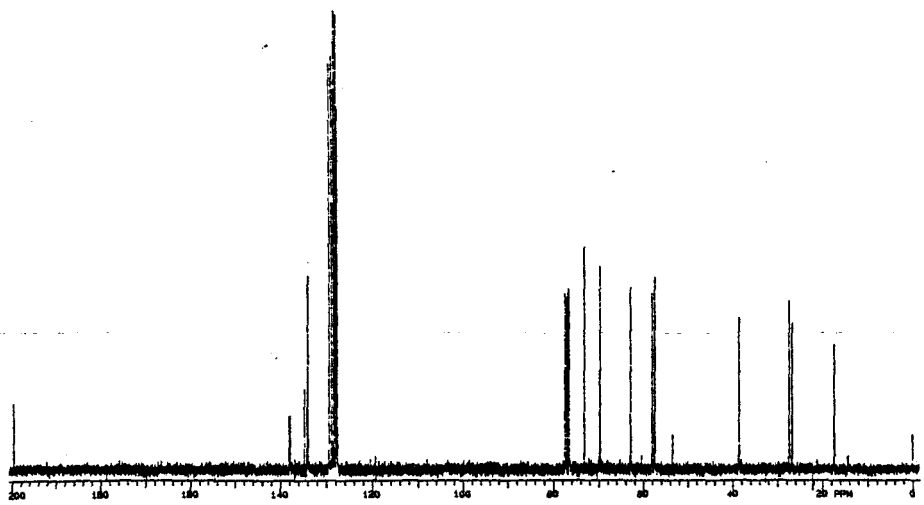

$^{1}$H NMR 1-benzyl-5-methyl-6-[3-benzyloxypropyl]piperidine



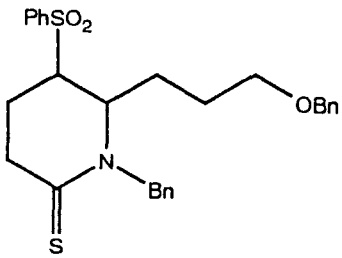

$^{1}$H NMR 1-benzyl-5-cyano-6-[3-benzyloxypropyl]piperidine



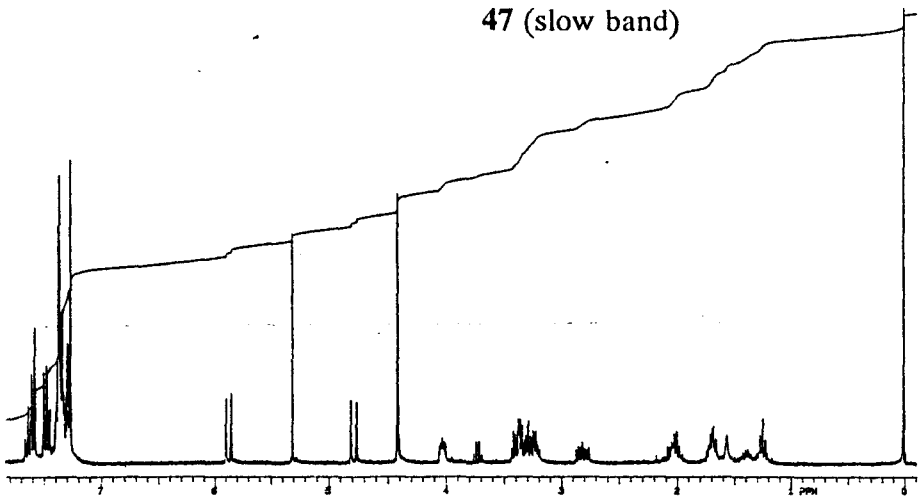



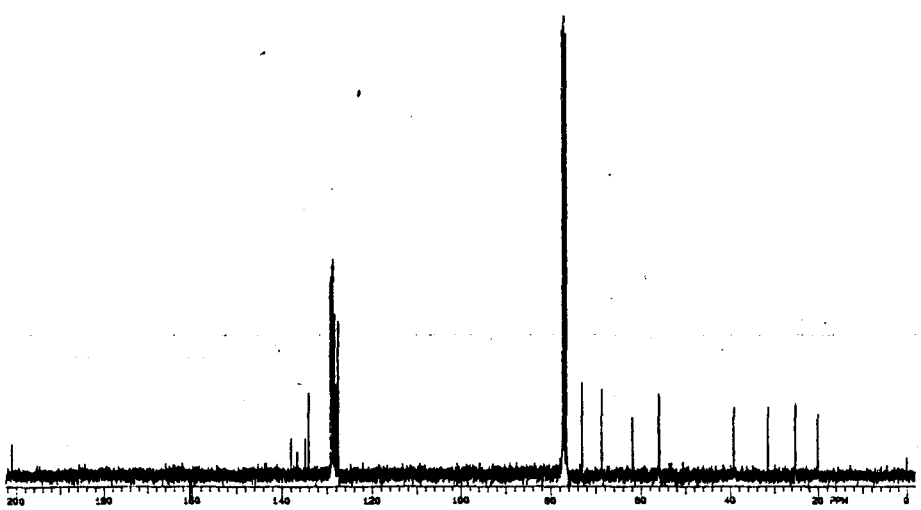



$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl] piperidi-2-thione (fast band)

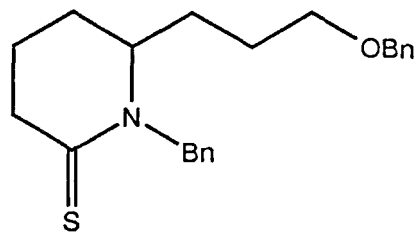



**47** (slow band)

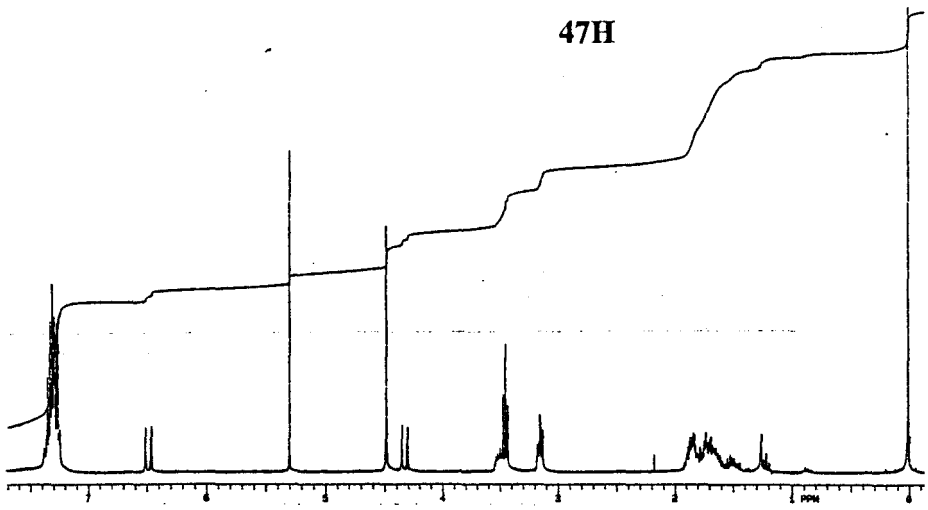


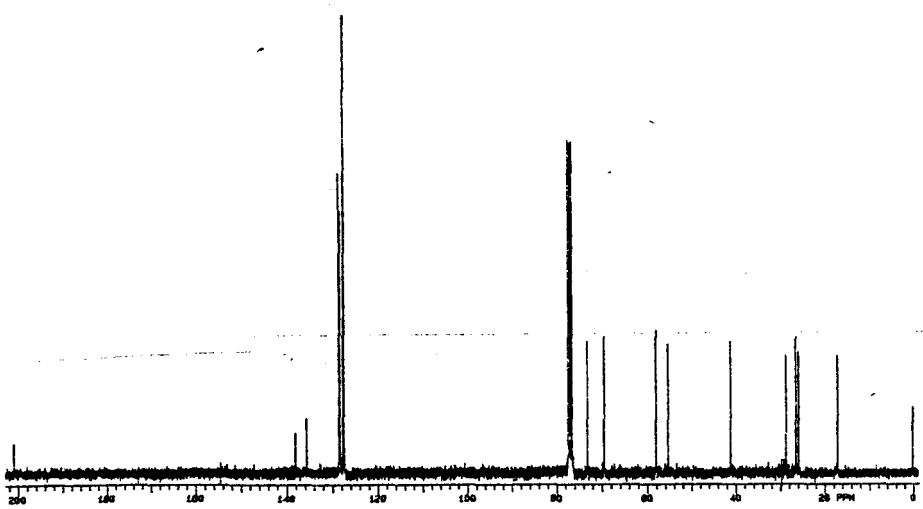


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl] piperidi-2-thione (slow band)

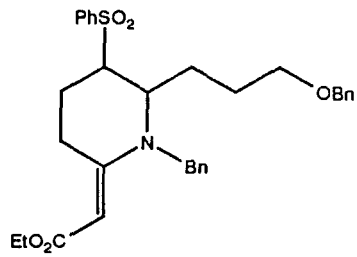



**47H**

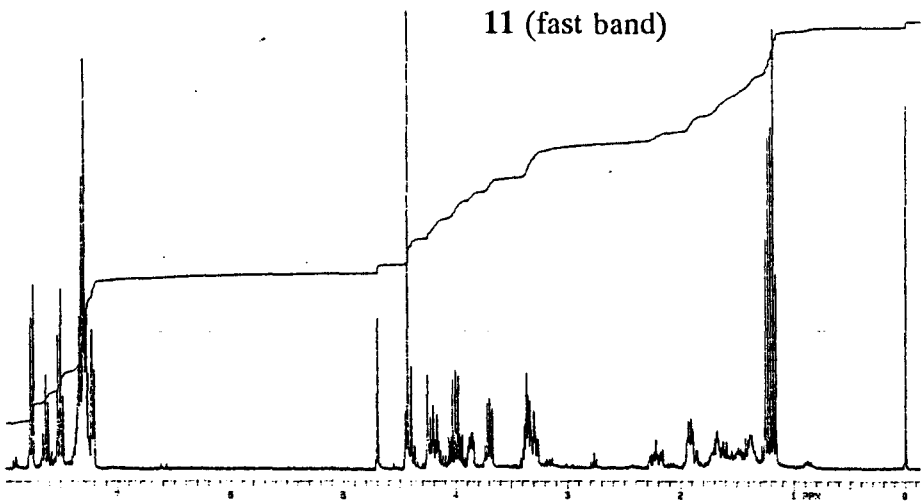


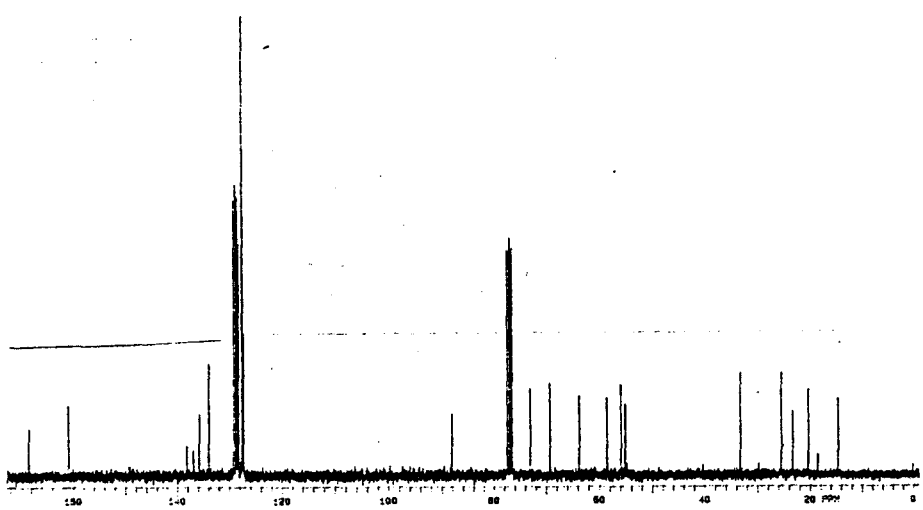


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[3-benzyloxypropyl]piperidi-2-thione

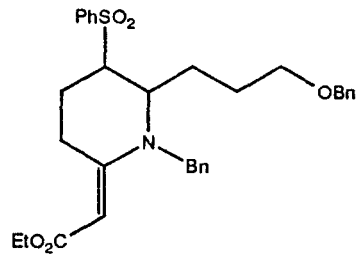



11 (fast band)

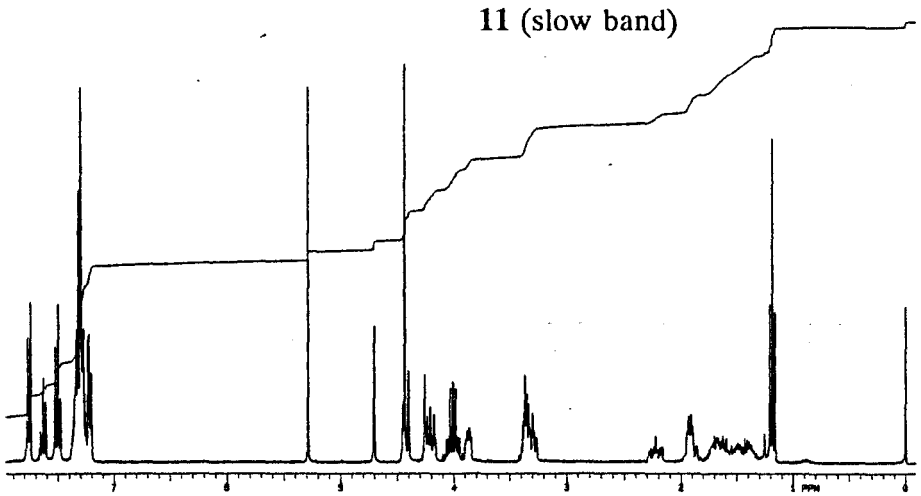


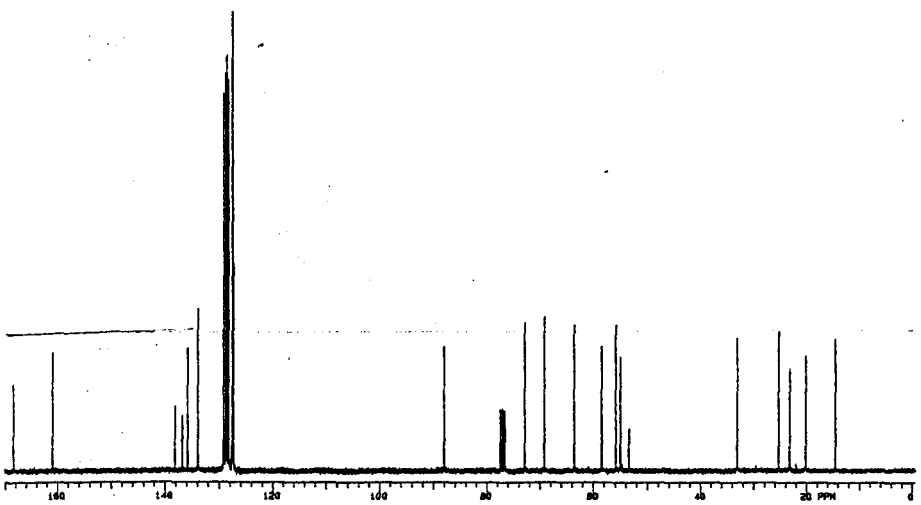


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methylidene]piperidine (fast band)

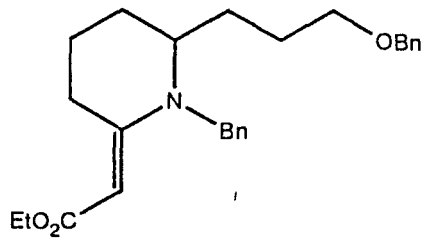



**11** (slow band)

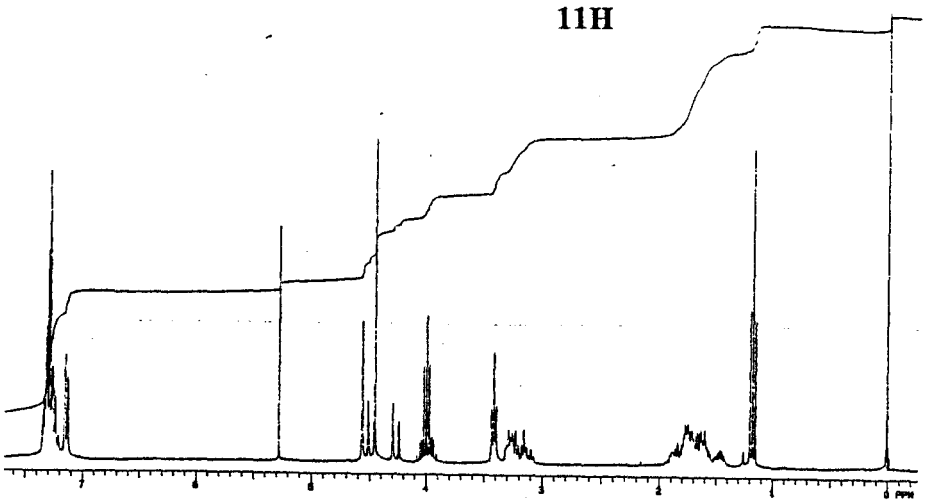


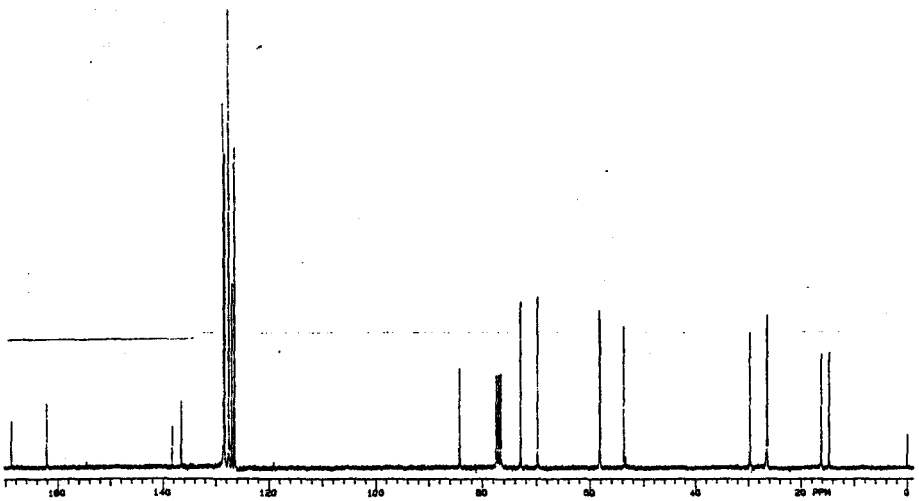


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methylidene]piperidine (slow band)

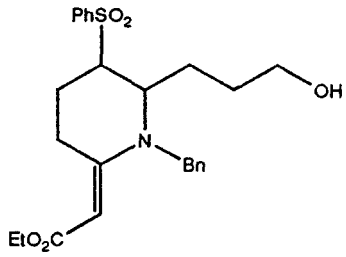



**11H**

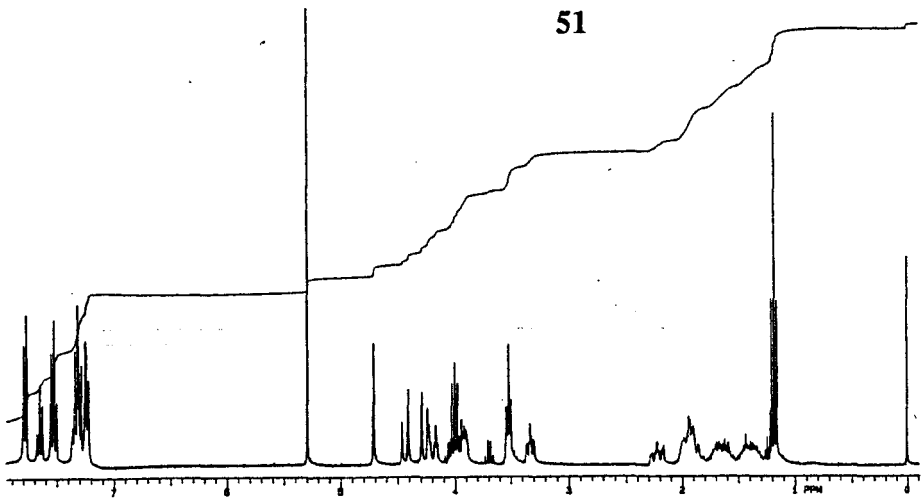


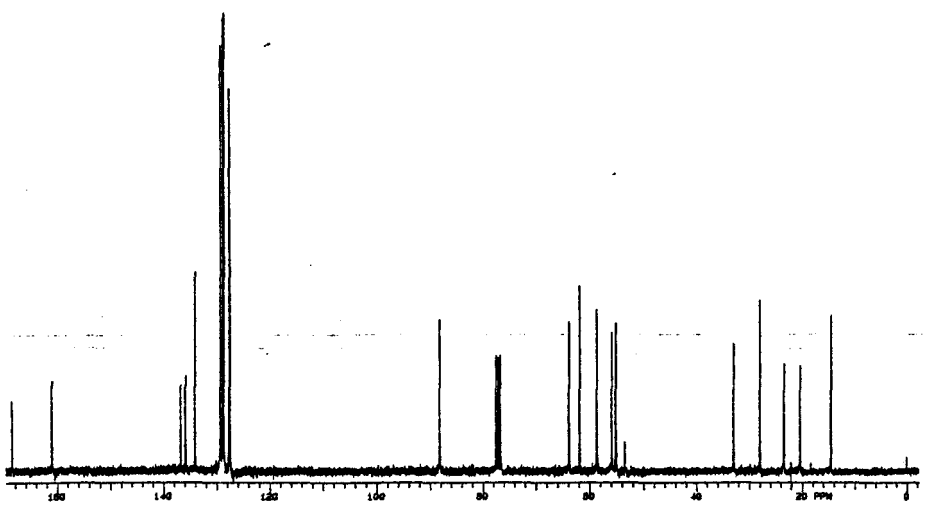


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methylidene]piperidine

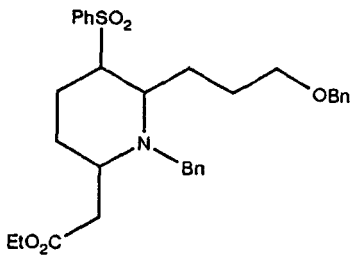


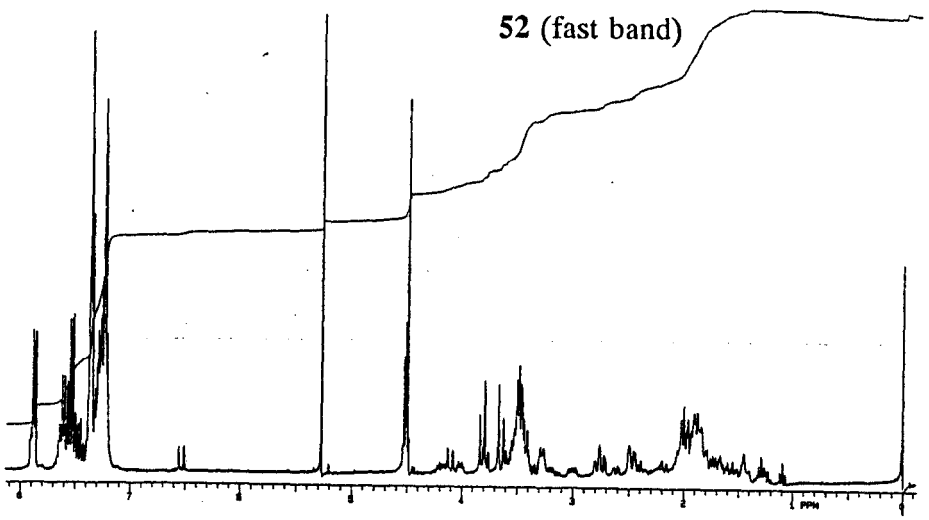

**51**

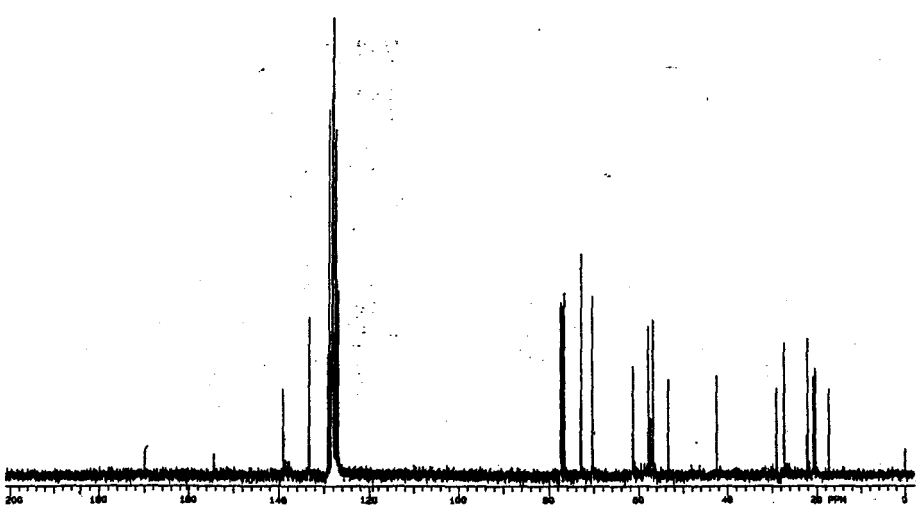




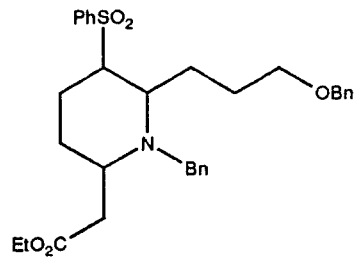
$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[hydroxypropyl]-2-[(ethoxycarbonyl)methylidene]piperidine



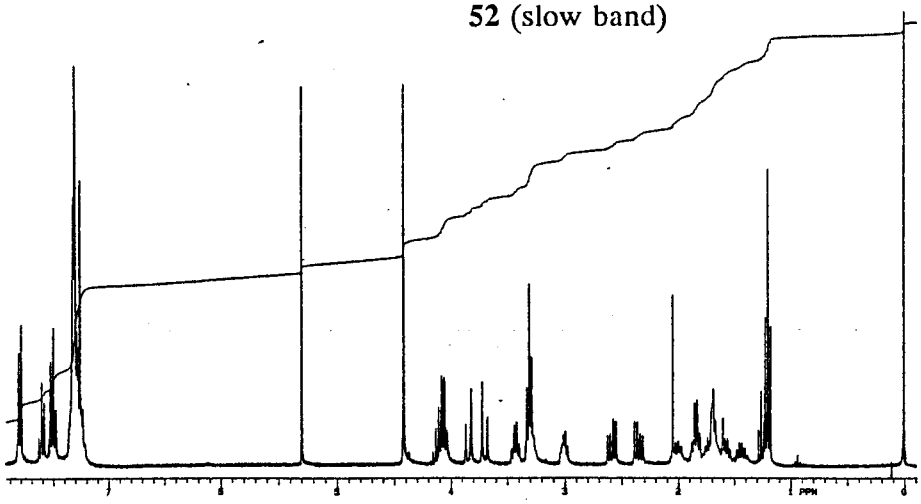



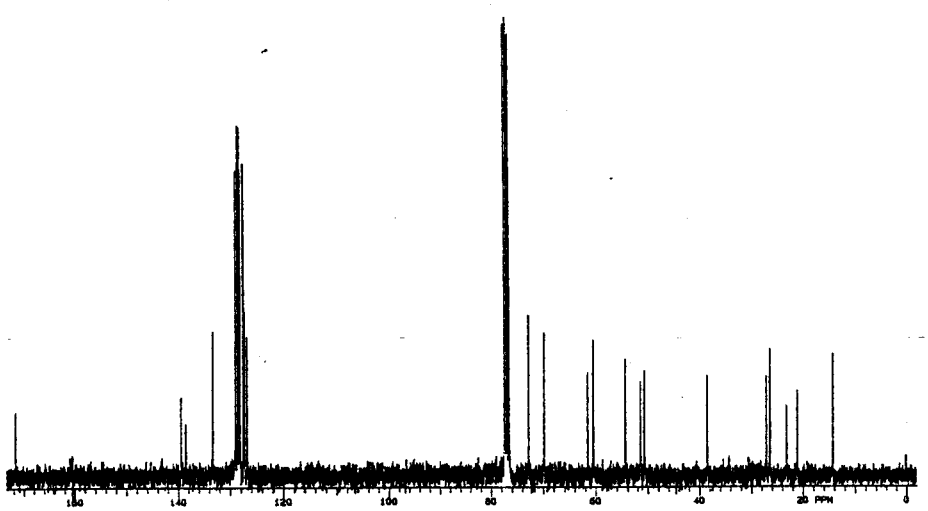



$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine (fast band)

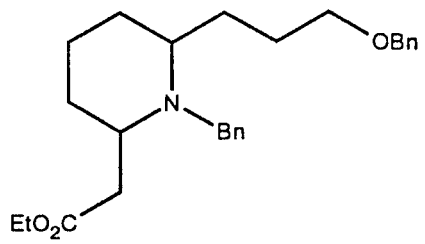



**52** (slow band)

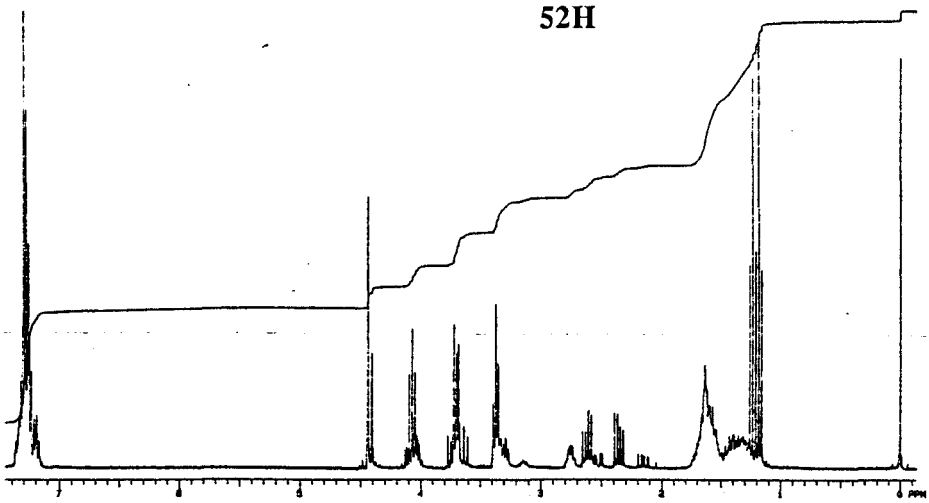


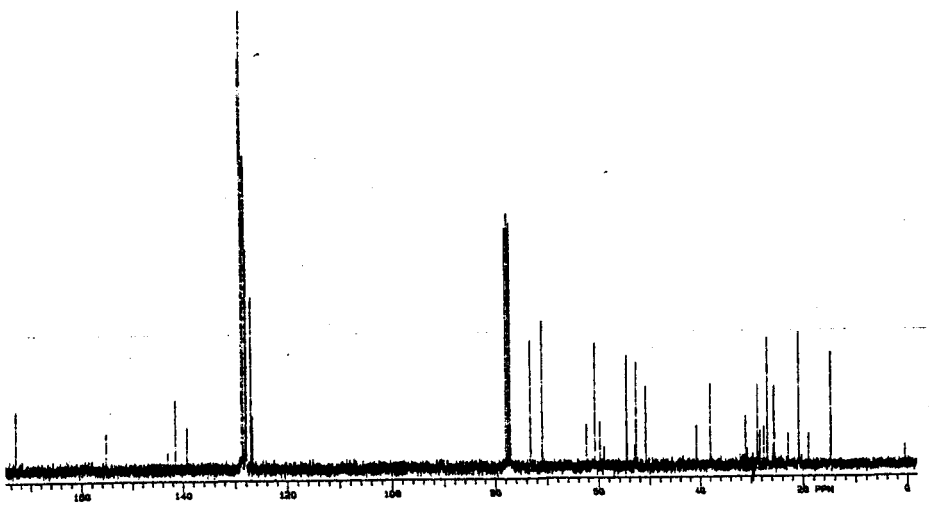


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-5-(phenylsulfonyl)-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine (slow band)

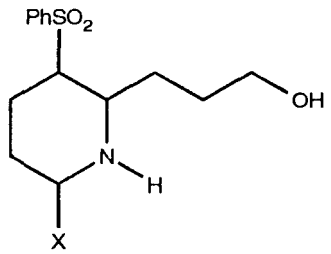



**52H**

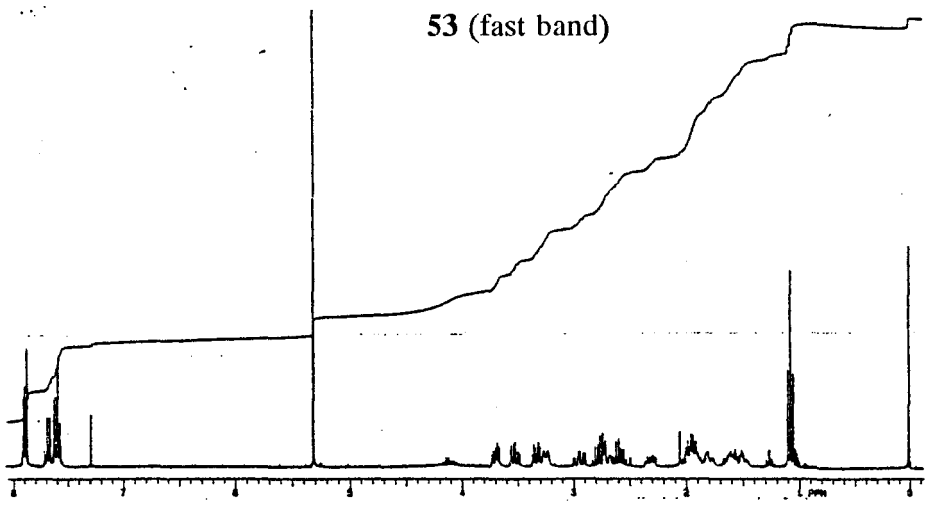


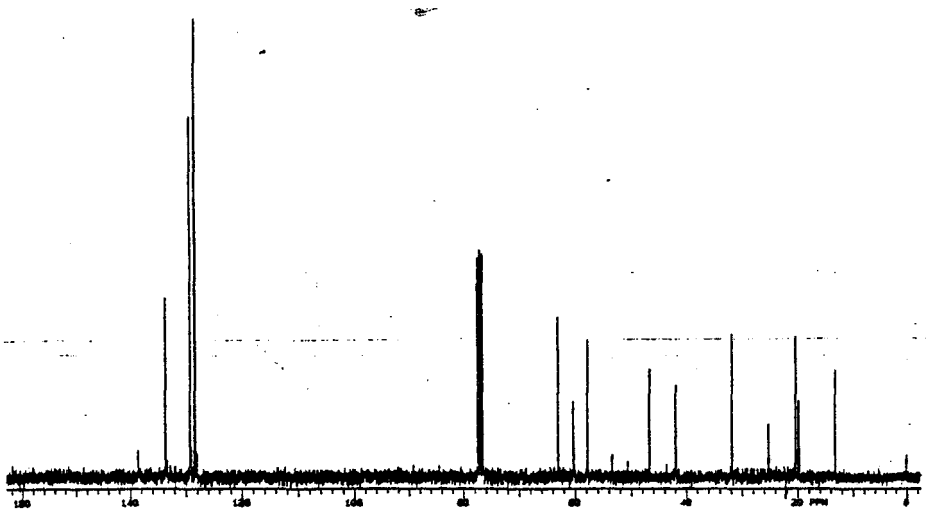


$^{1}H$ NMR and $^{13}C$ NMR 1-benzyl-6-[benzyloxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine

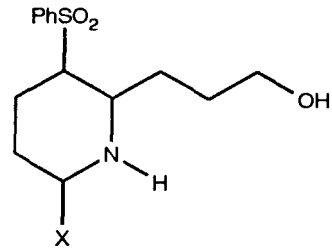



**53** (fast band)

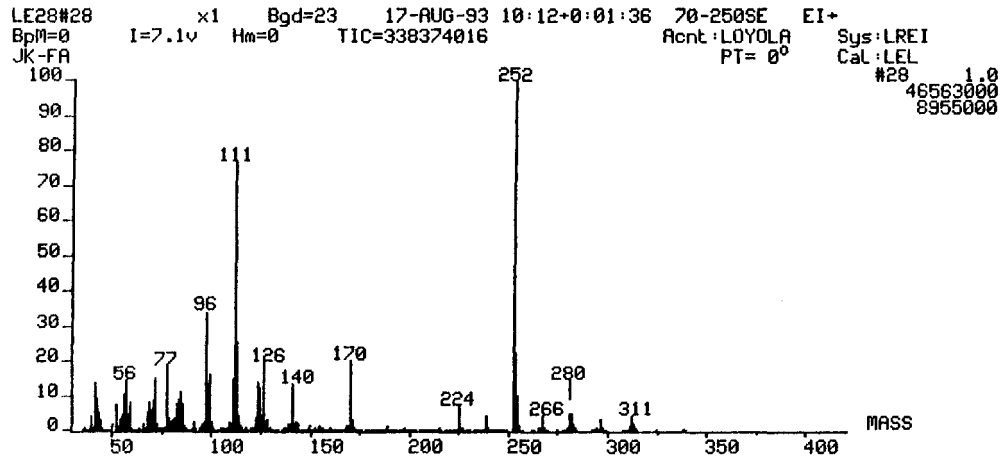


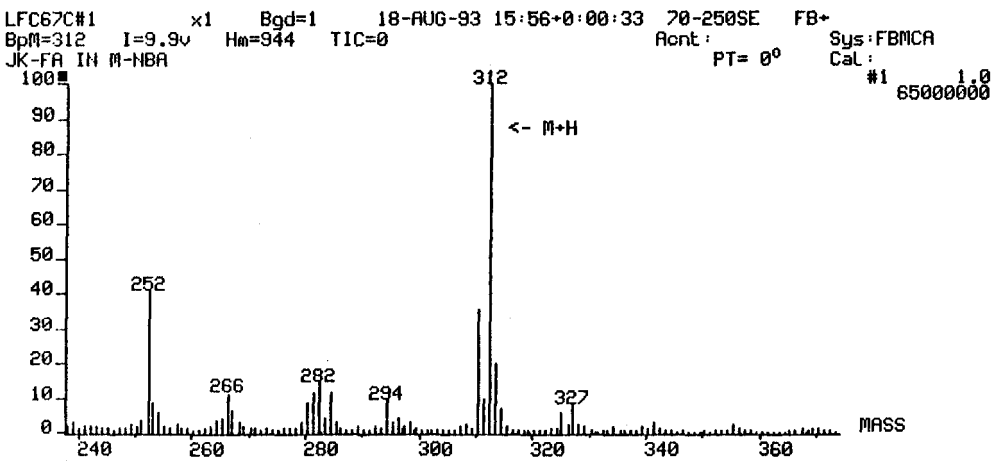


$^{1}H$ and $^{13}C$ NMR **53** (fast band)

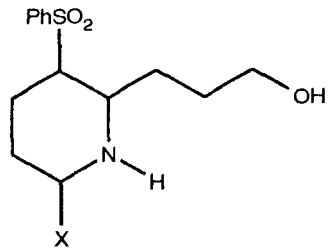



**53** (fast band)

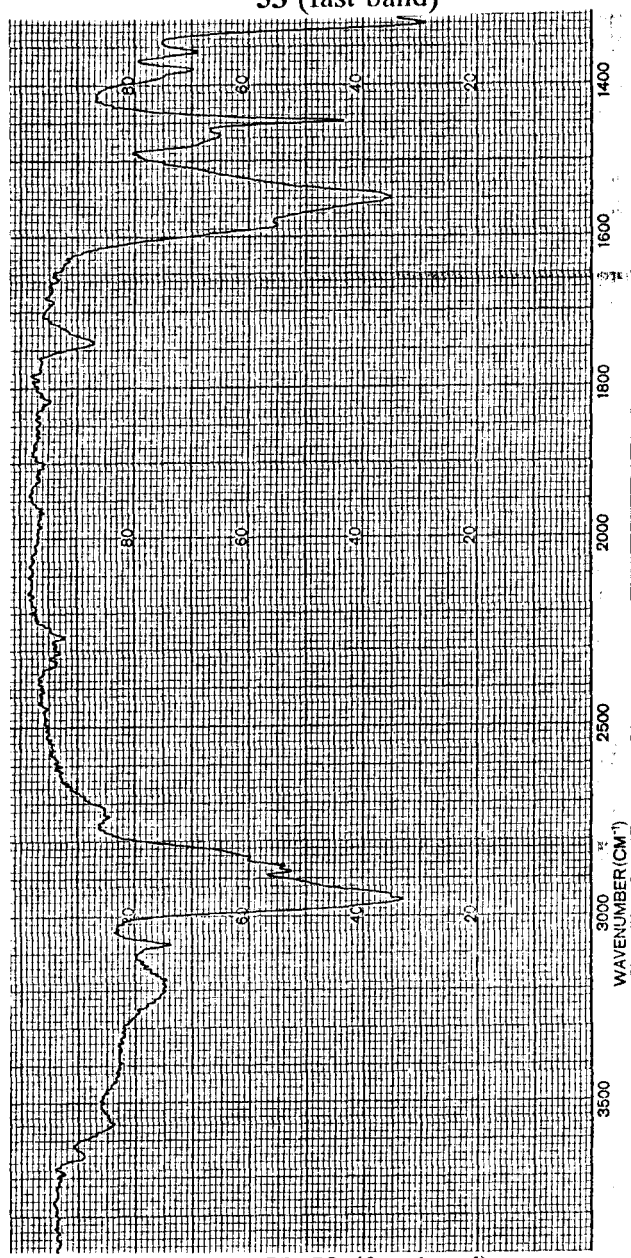


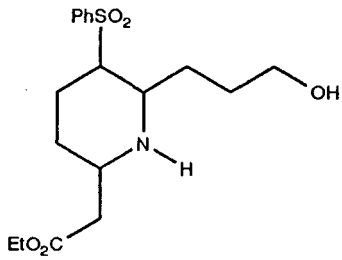

Electron impact (EI+) and fast atom bombardment (FAB) mass spectrum **53** (fast band)



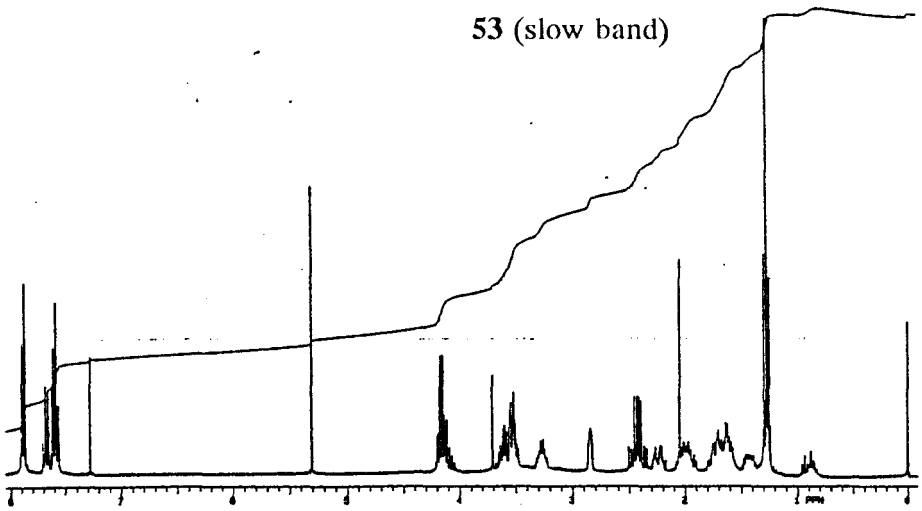

**53** (fast band)

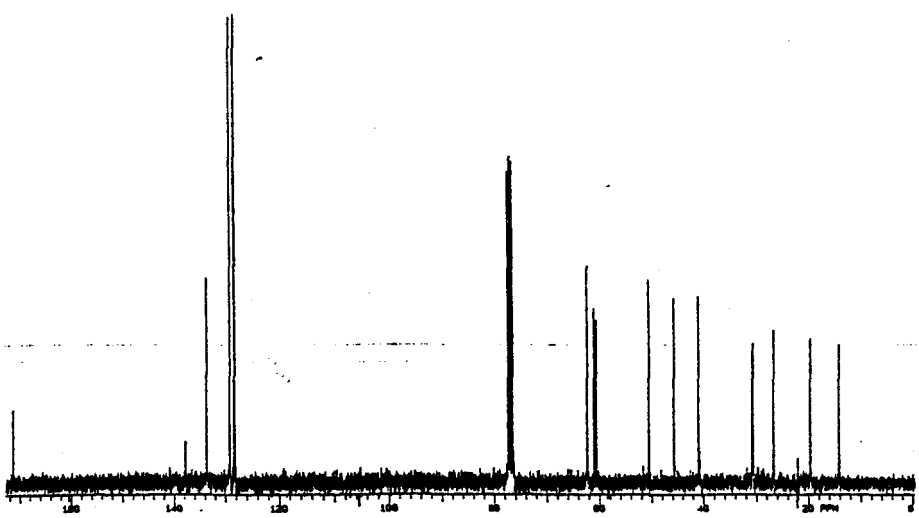



FT-IR **53** (fast band)

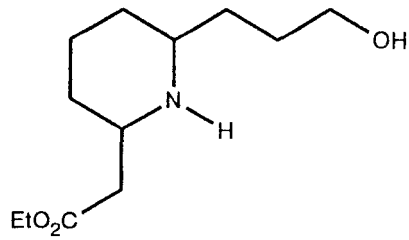



**53** (slow band)

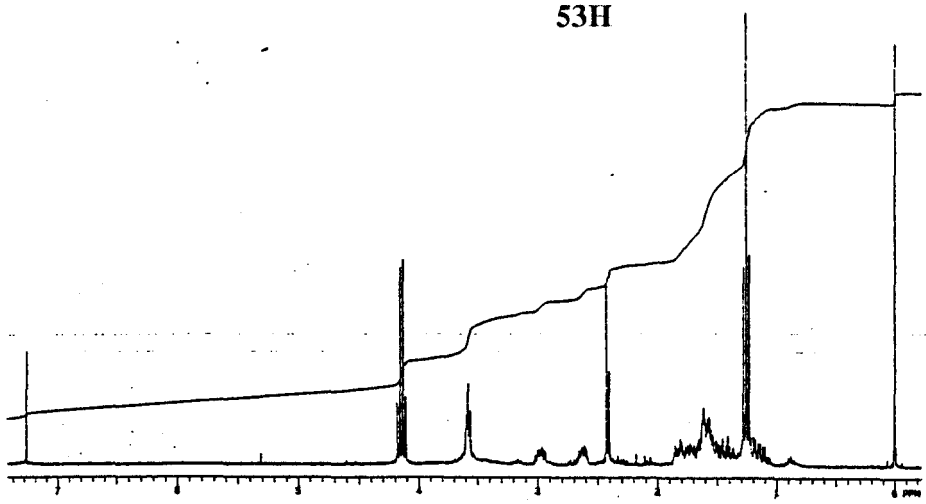


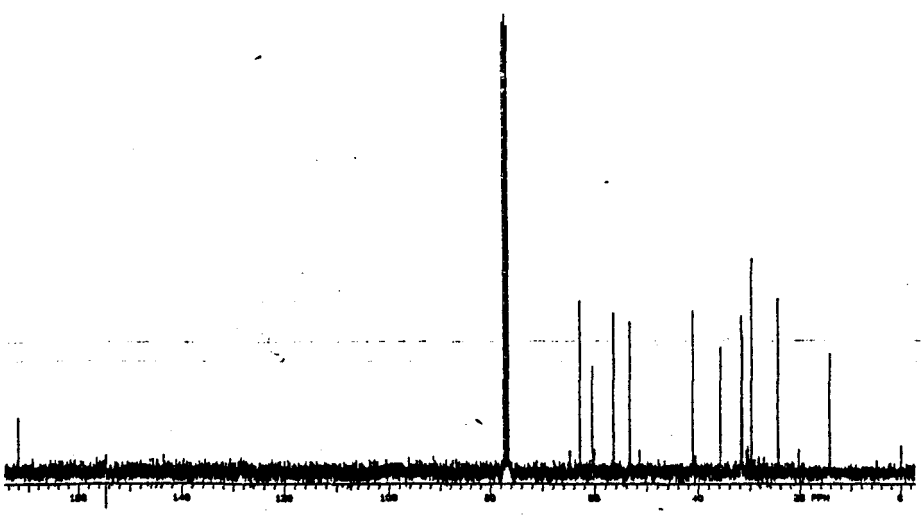


$^{1}H$ and $^{13}C$ NMR 5-(phenylsulfonyl)-6-[hydroxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine (slow band)

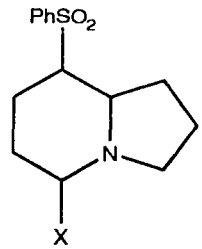



**53H**

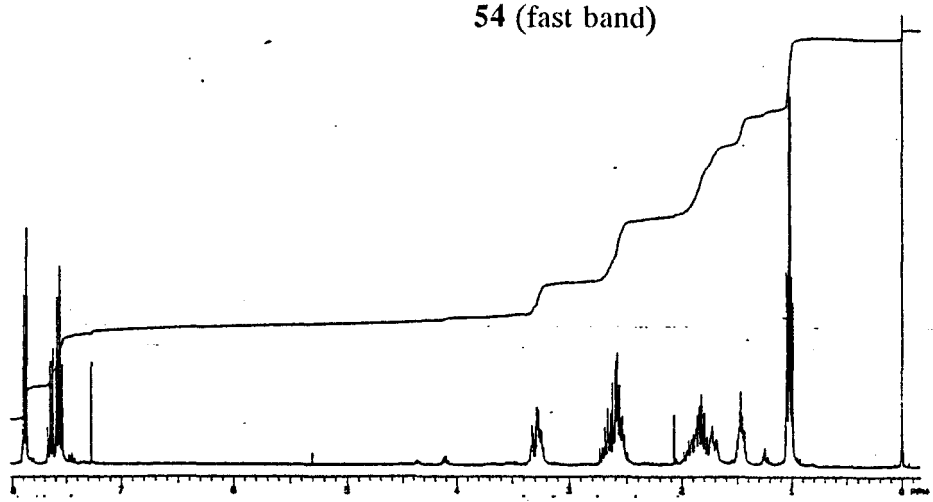


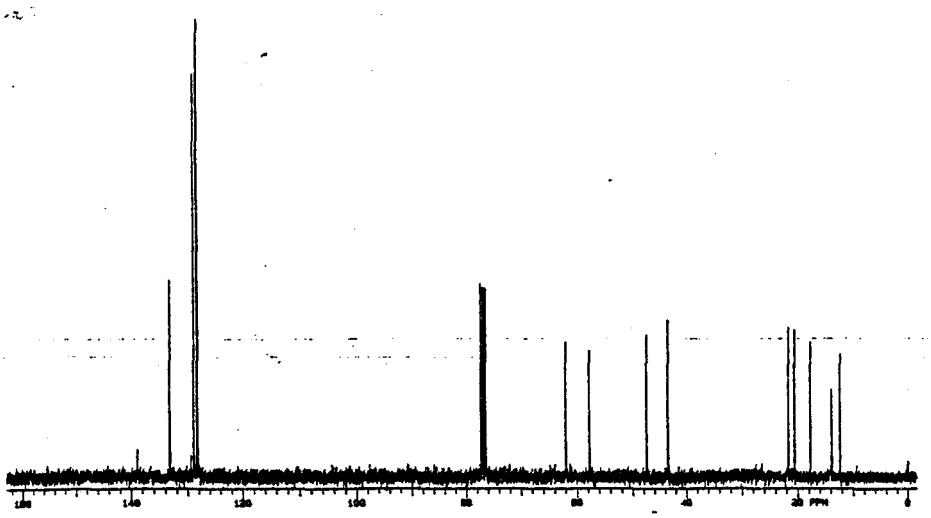


$^{1}H$ and $^{13}C$ NMR 6-[hydroxypropyl]-2-[(ethoxycarbonyl)methyl]piperidine

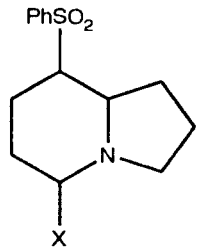



**54** (fast band)

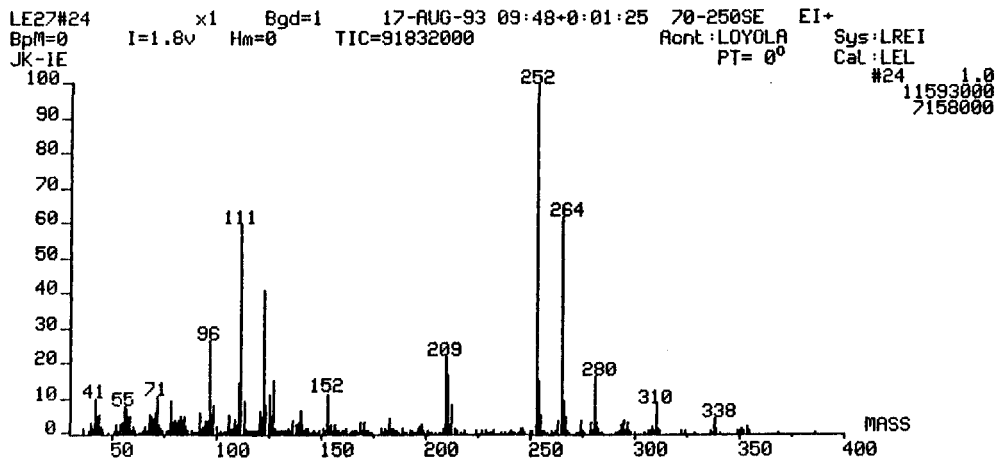


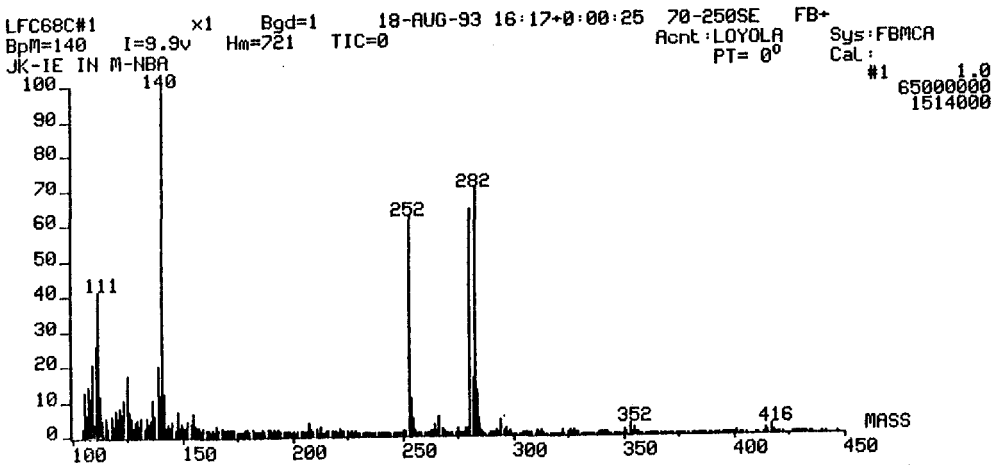


$^{1}H$ and $^{13}C$ NMR **54** (fast band)

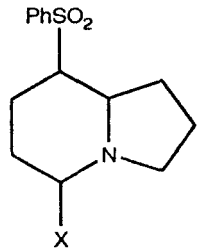



**54** (fast band)

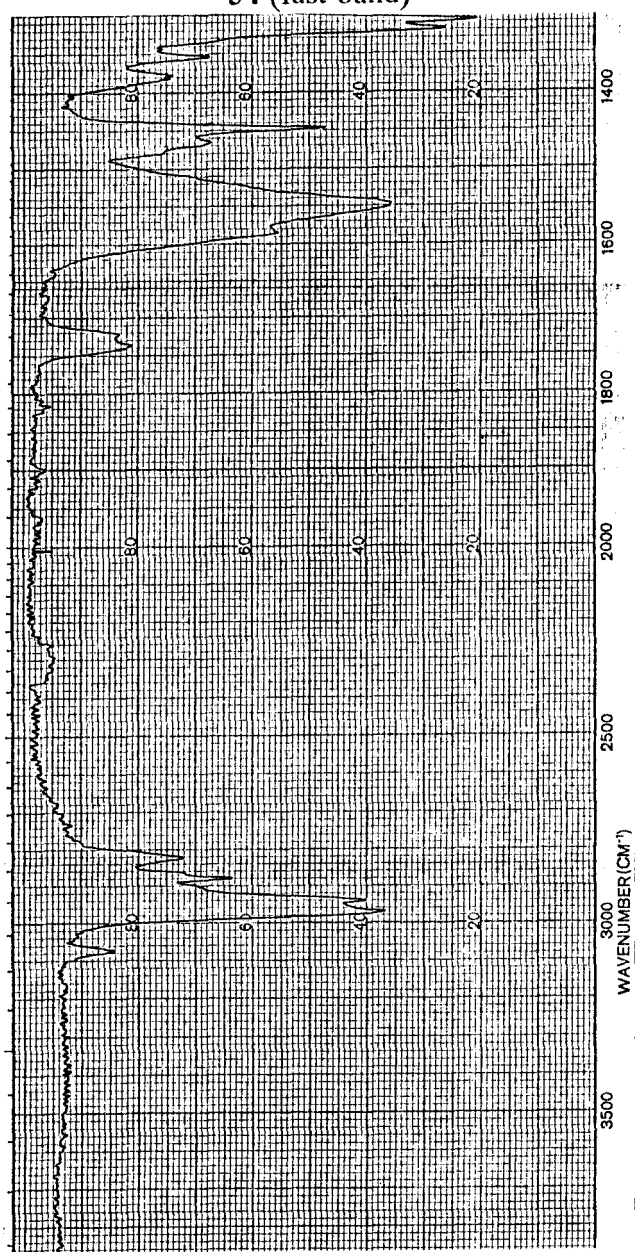


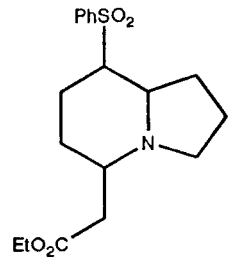

Electron impact (EI+) and fast atom bombardment (FAB) mass spectrum **54** (fast band)



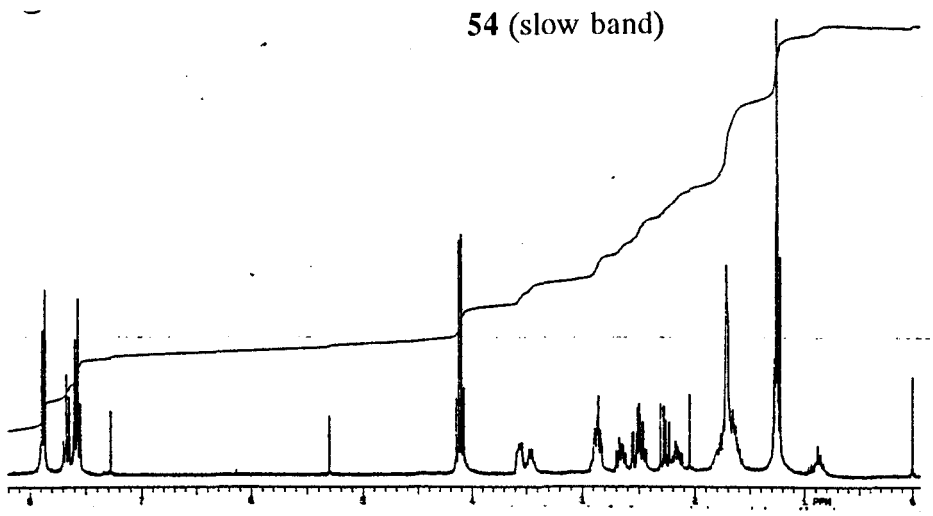

**54** (fast band)

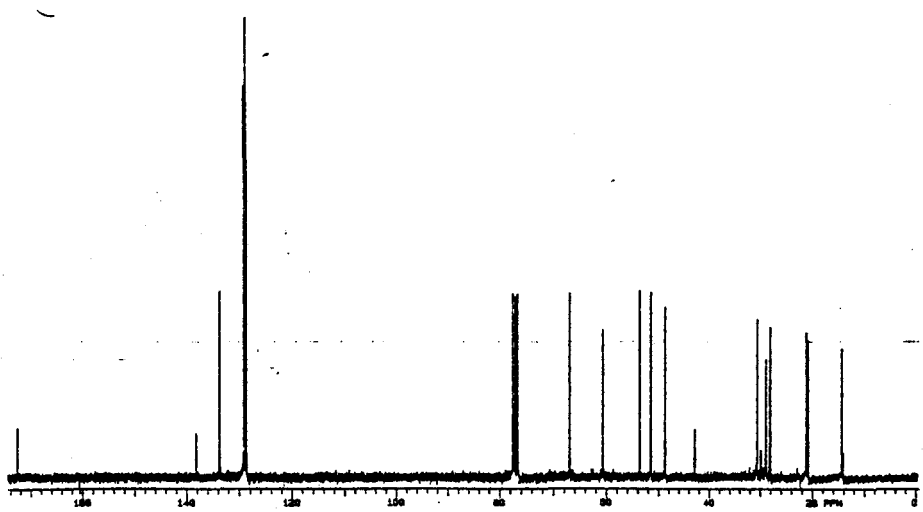



FT-IR **54** (fast band)

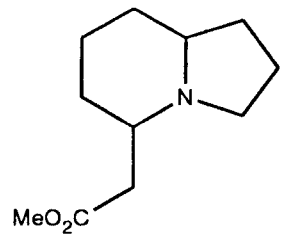



**54** (slow band)

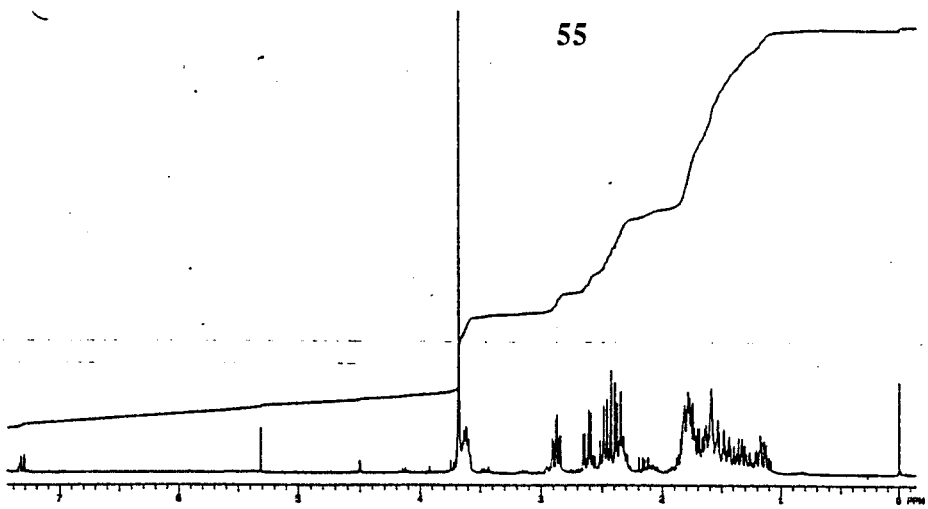


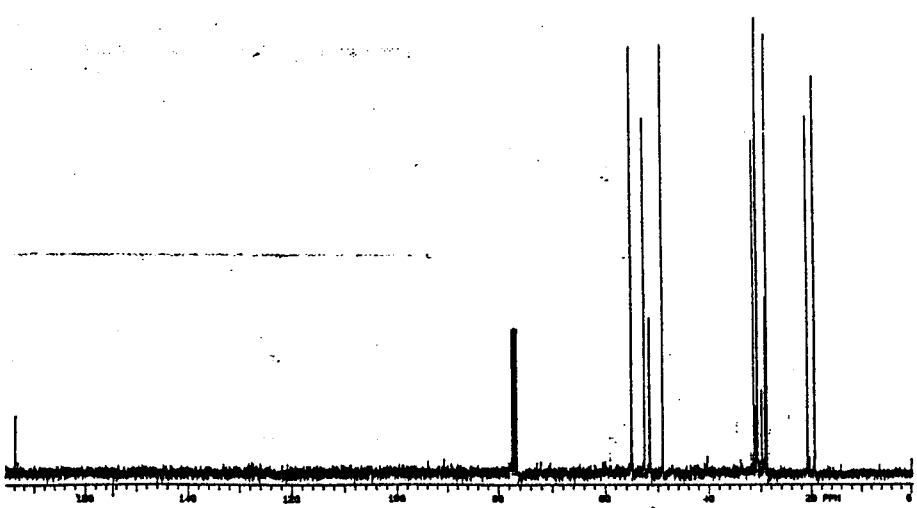


$^{1}H$ and $^{13}C$ NMR 8-(phenylsulfonyl)-5-[(ethoxycarbonyl)methyl] indolizidine (slow band)




55





$^{1}H$ and $^{13}C$ NMR 5-[(ethoxycarbonyl)methyl]indolizidine

## REFERENCES


1. Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* **1983**, *109*, 165.

2. Lavielle, G.; Sturtz, G. *Bull. Soc. Chem. Fr.* **1970**, 1369.

3. Warren, S.; Grayson, J.I.; Ernshaw, C.; Davidson, A.H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1452.

4. Asato, A.E.; Lui, R.S.H. *J. Am. Chem. Soc.* **1975**, *97*, 4128.

5. Pattenden, G.; Weedon, B.C.L. *J. Chem. Soc., Chem. Commun.* **1968**, 1984; 1997.

6. Surmatis, J.D.; Thommen, R. *J. Org. Chem.* **1969**, *34*, 559.

7. Ito, M.; Masahara, R.; Tsukida, K. *Tetrahedron Lett.* **1977**, 2767.

8. Edwards, J.A.; Scharz, V.; Fajkos, J.; Maddox, M.L.; Fried, J.H. *J. Chem. Soc., Chem. Commun.* **1971**, 292.

9. Wittig, G.; Geissler, G. *Liebigs. Ann. Chem.* **1953**, *44*, 1953.

10. Maercker, A. *Org. React.* **1965**, *14*, 270.

11. Wadsworth, W.S.; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

12. Wadsworth, W.S. *Org. React.* **1977**, *25*, 73.

13. Gosney, I.; Rowley, A.G. in *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J.I.G. Ed.; Academic Press: London, 1979, pp 17-153.

14. Julia, M.; Arnold, D. *Bull. Soc. Chim. Fr., Part II* **1973**, 746.

15. Arbuzov, A.E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.

16. Schweizer, E.E.; Shaffer, E.T.; Hughes, C.T.; Berninger, C.J. *J. Org. Chem.* **1966**, *31*, 2907.

17. Bhattacharya, A.K.; Thyagarjan, G. *Chem. Rev.* **1981**, *81*, 415.

18. Hafner, A.; Philipsborn, W.; Salzer, A. *Helv. Chim. Acta* **1986**, *69*, 1757.

19. Michaelis, A.; Becker, T. *Chem. Ber.* **1897**, *30*, 1003.

20. Engel, R. *Synthesis of Carbon Phosphorus Bonds*; CRC Press: Florida, 1988; pp 7-75.

21. Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239.

22. Lu, X.; Huang, J.; Zhu, J. *Acta Chimica. Sinica* **1985**, *43*, 702.

23. Lu, X.; Zhu, J. *Synthesis* **1986**, 563.

24. Janecki, T.; Bodalski, R. *Synthesis* **1990**, 799.

25. Hirao, T.; Masunaga, T.; Yamada, N.; Ohsiro, Y.; Agawa, T. *Bull. Chem. Soc. Japan.* **1982**, *55*, 909.

26. Hirao, T.; Hagihara, M.; Agawa, T. *Bull. Chem. Soc. Japan.* **1985**, *58*, 3104.

27. Corey, E.J.; Katzenellenbogen, J.A.; Gilman, N.W.; Roman, S.A.; Erickson, B.W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

28. Corey, E.J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 6636.

29. Corey, E.J.; Katzenellenbogen, J.A.; Roman, S.A.; Gilman, N.W. *Tetrahedron Lett.* **1971**, 1821.

30. Surmatis, J.D.; Thommen, R. *J. Org. Chem.* **1969**, *34*, 559.

31. Phillips, A.M.M.M.; Modro, T.A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1875.

32. Babler, J.H.; Schlidt, S.A. *Tetrahedron Lett.* **1992**, *33*, 7697.

33. Jacoby, D.; Celerier, J.P.; Petit, H.; Lhommet, G. *Synthesis* **1990**, 301 and references 11-14 cited therein.

34. Nalewajek, D.; Soriano, D.S. U.S. Patent 4 582 652, 1986.

35. For a review of the synthesis of vinyl phosphonates see Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333-349.

36. Czekanski, T.; Gross, H.; Costisella, B.J. *J. Prakt. Chem.* **1982**, *324*, 537.

37. Carey, F.A.; Court, A.S. *J. Org. Chem.* **1972**, *37*, 939.

38. Wysocki, D.C. Ph.D. Thesis, University of Pittsburgh, 1967.

39. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

40. Tebby, J.C. in *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J.G.; Quin, L.D.; Eds.; VCH Publishers: Florida, 1987; pp 1-60.

41. Maier, L. *Z. Anorg. Allg. Chem.* **1972**, *394*, 117.

42. Rambaud, M.; Vecchio, A.; Villieras, J. *Synth. Commun.* **1984**, *14*, 833.

43. Spassov, S.L.; Markova, L.; Mondeshka, D.M.; Tancheva, Ch.N.; Angelov, Ch. M. *Magn. Res. Chem.* **1985**, *23*, 578.

44. Hine, J. *Structural Effects on Equilibria in Organic Chemistry;* Wiley: New York; 1975, pp 257-283.

45. Gerber, J.P.; Modro, T.A.; Wagener, C.C.P.; Zwierzak, A. *Heteroatom Chem.* **1991**, *2*, 643.

46. Bordwell, F.G. *Acc. Chem. Res.* **1988**, *21*, 456.

47. Koizumi, T.; Tanaka, N.; Iwataa, M.; Yoshii, E. *Synthesis* **1982**, 917.

48. Drew, J.; Letellier, M.; Morand, P.; Szabo, A.G. *J. Org. Chem.* **1987**, *52*, 4047.

49. Hirao, T.; Ohshiro, Y.; Kerokawa, K.; Agawa, T. *Yukagaku* **1983**, *32*, 274.

50. Canevet, C.; Roder, T.; Vostrowsky, O.; Bestmann, H. *Chem. Ber.* **1980**, *113*, 1115.

51. Howard, A.S.; Michael, J.P. in *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol 28, p. 185.

52. Elbien, A.D.; Molyneux, R.J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1987; Vol 5, pp. 1-54.

53. Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.

54. Fellows, L.E.; Nash, R.J. *Sci. Progress* **1990**, *74*, 245.

55. Dennis, J. *Cancer Res.* **1986**, *46*, 5131.

56. Palmarczyk, G.; Elbein, A.D. *Biochem. J.* **1985**, *227*, 795.

57. Sasak, V.; Ordovas, K.; Elbein, A.; Berninger, R. *Biochem. J.* **1986**, *232*, 759.

58. Cook, N.; Evans, S.; Fellows, L.; Peters, T. *Biochem. Soc. Trans.* **1986**, *14*, 1053.

59. Humphries, M.; Matsumoto, K.; White, S.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.

60. Trungnan, G.; Rousset, M.; Zweibaun, A. *Fed. European Biochem. Soc.* **1986**, *195*, 28.

61. Pan, Y.; Hori, H.; Saul, R.; Sanford, B.; Molyneux, R.; Elbein, A. *Biochemistry* **1983**, *922*, 3975.

62. Merkle, R.; Elbein, A.; Heifetz, A. *J. Biol. Chem.* **1975**, *260*, 1083.

63. Schlesinger, S.; Koyama, A.; Malfer, C.; Gee, S.; Schlesinger, M. *Virus Res.* **1985**, *2*, 139.

64. Schwarz, P.; Elbein, A. *J. Biol. Chem.* **1985**, *260*, 14452.

65. Repp, R.; Tamura, T.; Boschek, C.; Wege, H.; Schwarz, R.; Niemann, H.J. *J. Biol. Chem.* **1985**, *260*, 15873.

66. Dagani, R. *Chem. Eng. News* **1987**, *65*, 41.

67. Dagani, R. *Chem. Eng. News* **1987**, *65*, 25.

68. Cartwright, D.; Gardiner, R.A.; Rinehart, K.L. *J. Am. Chem. Soc.* **1970**, *92*, 7615.

69. Daly, J.W.; Myers, C.W. *Science* **1967**, *156*, 970.

70. Daly, J.W.; Garraffo, H.M.; Spande, T.F. *The Alkaloids*; Cordell, G.A., Ed.; Academic Press: New York, 1993; Vol 43, pp. 185-288.

71. Daly, J.W. *Progress in the Chemistry of Natural Products*; Herz, W.; Grisebach, H.; Kirby, G.W., Eds.; Springer-Verlag: New York, 1982; pp. 283-340.

72. Daly, J.W.; Spande, T.F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1986; Vol 4, p. 1.

73. Daly, J.W.; Brown, G.B.; Mensah-Dwumah, M.; Myers, C.W. *Toxicon* **1978**, *16*,

163.

74. Daly, J.W.; Myers, C.W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023.

75. Daly, J.W.; Highet, R.J.; Myers, C.W. *Toxicon* **1984**, *22*, 905.

76. Tokuyama, T.; Tsujita, T.; Shimada, A.; Garraffo, H.M.; Spande, T.F.; Daly, J.W. *Tetrahedron* **1991**, *47*, 5401.

77. Mensah-Dwumah, M.; Daly, J.W. *Toxicon* **1968**, *16*, 189.

78. Aronstam, R.S.; Daly, J.W.; Spande, T.F.; Narayanan, T.K.; Albuquerque, E.X. *Neurochemical Res.* **1986**, *11*, 1227.

79. Rajeswari, S.; Chandrasekharan, S.; Govindachari, T.R. *Heterocycles* **1987**, *25*, 659.

80. Michael, J.P. *Nat. Prod. Rep.* **1993**, *10*, 51.

81. Lamberton, J.A. in *The Alkaloids, Specialists Periodical Reports*; Grundon, M.F., Ed., The Royal Society of Chemistry, London, **1979**, *9*, 67; **1980**, *10*, 63; **1981**, *11*, 59; **1982**, *12*, 69.

82. Kibayashi, C. *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1992; Vol 2, pp. 229-275.

83. Raub, M.F.; Cardellina, J.H.; Spande, T.F. *Tetrahedron Lett.* **1992**, *33*, 2257.

84. Jefford, C.W.; Wang, J.B. *Tetrahedron Lett.* **1993**, *34*, 3119.

85. Polniaszek, R.P.; Belmont, S.E. *J. Org. Chem.* **1990**, *55*, 4688.

86. Oliver, J.E.; Sonnet, P.E. *J. Org. Chem.* **1974**, *39*, 2662.

87. Sonnet, P.E.; Oliver, J.E. *J. Heterocyclic Chem.* **1975**, *12*, 289.

88. Macdonald, T.L. *J. Org. Chem.* **1980**, *45*, 193.

89. Stevens, R.V.; Lee, A.W.M. *J. Chem. Soc., Chem. Commun.* **1982**, 102.

90. Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513.

91. Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094.

92. Ito, M.; Kibayashi, C. *Tetrahedron* **1991**, *47*, 9329.

93. Angle, S.R.; Breitenbucher, J.G. *Tetrahedron Lett.* **1993**, *34*, 3988.

94. McGrane, P.L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323.

95. Macdonald, T.L. *J. Org. Chem.* **1980**, *45*, 193.

96. Royer, J.; Husson, H.P. *Tetrahedron Lett.* **1985**, *26*, 1515.

97. Brandi, A.; Cordero, F.; Querci, C. *J. Org. Chem.* **1989**, *54*, 1748.

98. Codero, F.; Brandi, A.; Querci, C.; Goti, A.; De Sarlo, F.; Guarna, A. *J. Org. Chem.* **1990**, *55*, 1762.

99. Zeller, E.; Grierson, D.S. *Heterocycles* **1988**, *27*, 1575.

100. Nakagawa, Y.; Stevens, R.V. *J. Org. Chem.* **1988**, *53*, 1871.

101. Iida, H.; Watanabe, Y.;Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534.

102. Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088.

103. Stevens, R.V.; Lee, A.W.M. *J. Chem. Soc., Chem. Commun.* **1982**, 103.

104. Machiwaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178.

105. Taber, D.F.; Deker, P.B.; Silverberg, L.J. *J. Org. Chem.* **1992**, *57*, 5990.

106. Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405.

107. Tokuyama, T.; Tsujita, T.; Garraffo, H.M; Spande, T.F.; Daly, J.W. *Tetrahedron* **1991**, *47*, 5401.

108. Smith, A.L.; Williams, S.F.; Holmes, A.B.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696.

109. Holmes, A.B.; Smith, A.L.; Willians, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

110. Collins, I.; Fox, M.E.; Holmes, A.B.; Williams, S.F.; Baker, R.; Forbes, I.J.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 175.

111. For a review of the use of acyliminium ions in alkaloid synthesis see Hart, D.J.

in *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1988; Vol 6, pp. 227-296.

112. Polniaszek, R.P.; Belmont, S.E. *J. Org. Chem.* **1991**, *56*, 4868.

113. Gnecco, D.; Marazano, C.; Das, B.C. *J. Chem. Soc., Chem. Commun.* **1991**, 625.

114. Shishido, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1237.

115. Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.

116. Thompson, C.M.; Green D.L.C. *Tetrahedron* **1991**, *47*, 4223.

117. Thompson, C.M. *Tetrahedron Lett.* **1987**, *28*, 4243.

118. Thompson, C.M.; Frick, J.A. *J. Org. Chem.* **1989**, *54*, 890.

119. Williams, K.; Thompson, C.M. *Synth. Commun.* **1992**, *22*, 239.

120. Thompson, C.M.; Green D.L.C.; Kubas, R. *J. Org. Chem.* **1988**, *53*, 5389.

121. Stevens, R.V. in *The Total Synthesis of Natural Products*; Ap-Simon, J., Ed.; Wiley: New York, 1977; Vol 3.

122. Green, D.L.C.; Thompson, C.M. *Tetrahedron Lett.* **1991**, *32*, 5051.

123. Green, D.L.C. Ph.D. Thesis, Loyola University of Chicago, 1992.

124. Thompson, C.M. *Heterocycles* **1992**, *34*, 979.

125. Hwu, J.R. *J. Org. Chem.* **1983**, *48*, 4432.

126. Cava, M.P.; Levinson, M.I. *Tetrahedron* **1985**, *41*, 5061.

127. Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529.

128. Fletcher, H.G. *Methods Carbohydr. Chem.* **1963**, *2*, 166.

129. Harding, K.E.; Jones, M.W. *Heterocycles* **1987**, *28*, 663.

130. Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.

131. Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

132. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165.

133. Gunther, H. *NMR Spectroscopy*; Wiley: New York, 1980; p. 112.

134. Sperber, N.; Zaugg, H.E.; Sandstrom, W.M. *J. Am. Chem. Soc.* **1947**, *69*, 915.

135. Winterfeldt, E. *Synthesis* **1975**, 617.

136. Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* **1985**, *50*, 3885.

137. Bruylants, A.; Feytmants-de Medicis, E. in *The Chemistry of the Carbon Nitrogen Double Bond*; Patia, S., Ed.; Wiley: New York, 1970; p 465.

138. Evans, D.A.; Ellman, J.A.; Dorow, R.L. *Tetrahedron Lett.* **1987**, *28*, 1123.

139. Borch, R.F. *Tetrahedron Lett.* **1968**, 61.

140. Dayagi, S.; Degani, Y. in *The Chemistry of the Carbon Nitrogen Double Bond*; Patia, S., Ed.; Wiley: New York, 1970; p 61.

141. Grierson, D. *Org. React.* **1990**, *39*, 85.

142. Pine, S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* **1985**, *50*, 1212.

143. Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1.

144. Shiosaki, K. in *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I.; Eds.; Pergamon Press: New York, 1991; p 865.

145. Clark, J. in *The Chemistry of the Carboxylic Acid and Esters*; Patai, S., Ed.; Wiley: New York, 1969; p 589, and references therein.

146. Olah, G.A.; Surya Prakash, G.K. in *Advances in Silicon Chemistry*; Larson, G.L., Ed.; JAI Press: Greenwich, 1991; p 1.

147. Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, *42*, 3761.

148. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.

149. Moffet, R.B. *Org. Syn. Coll. Vol. 4*, **1963**, 834.

150. Brown, H.C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.

151. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1988.

152. Shriver, D.F.; Drezdzon, M.A. *The Manipulation of Air Sensitive Compounds*; Wiley: New York, 1986.

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